L Number	Hits	Search Text	DB	Time stamp
1	14	inflammat$3 adj breast adj cancer	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM_TDB	2002/09/23 12:31
2	13363	breast adj cancer	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM_TDB	2002/09/23 12:30
3	3	(inflammat$3 adj breast adj cancer) and xenograft	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM_TDB	2002/09/23 12:35
4	195	(breast adj cancer) same xenograft	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM_TDB	2002/09/23 12:34
5	4	(breast adj cancer) same xenograft same inflammat$3	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM_TDB	2002/09/23 12:34
6	665	(breast adj cancer) same inflammat$3	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM_TDB	2002/09/23 12:34
7	105	((breast adj cancer) same inflammat$3) and xenograft	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM_TDB	2002/09/23 12:35
8	28	(((breast adj cancer) same inflammat$3) and xenograft) and @ay<2000	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM_TDB	2002/09/23 12:35

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE' ENTERED AT 12:58:34 ON 23 SEP 2002

L1	792	S INFLAMMAT### BREAST CANCER
L2	29	S L1 (P) XENOGRAFT
L3	10	DUP REM L2 (19 DUPLICATES REMOVED)
L4	249147	S BREAST CANCER
L5	2022	S L4 (P) XENOGRAFT
L6	1201	S L4 (10A) INFLAMMAT###
L7	29	S L6 (P) XENOGRAFT
L8	10	DUP REM L7 (19 DUPLICATES REMOVED)
L9	10	DUP REM L3 L8 (10 DUPLICATES REMOVED)
L10	79	S L1 AND REVIEW
L11	49	DUP REM L10 (30 DUPLICATES REMOVED)
L12	9	S L11 AND PY>1998
L13	0	S L11 AND ?CADHERIN
L14	17	S L1 AND ##CADHERIN
L15	0	S L11 AND ##CADHERIN
L16	9	DUP REM L14 (8 DUPLICATES REMOVED)
L17	26	S L1 AND P53
L18	11	DUP REM L17 (15 DUPLICATES REMOVED)
L19	7	S L1 AND EGFR
L20	4	DUP REM L19 (3 DUPLICATES REMOVED)
L21	13	DUP REM L18 L20 (2 DUPLICATES REMOVED)
L22	17	S L1 AND MUC#
L23	17	S L1 AND MUC##
L24	8	DUP REM L23 (9 DUPLICATES REMOVED)
L25	19	DUP REM L21 L24 (2 DUPLICATES REMOVED)
L26	79	S L1 AND (ESTROGEN RECEPTOR OR PROGESTERONE RECEPTOR)
L27	38	DUP REM L26 (41 DUPLICATES REMOVED)
L28	48	DUP REM L25 L27 (9 DUPLICATES REMOVED)
L29	26	S L28 AND PY<2000
L30	41479	S XENOGRAFT
L31	2523	S L30 AND BREAST CANCER
L32	2284	S L31 AND (ANIMAL MODEL OR MICE OR PIG OR RAT OR ANIMAL)
L33	57	S L32 AND REVIEW
L34	45	DUP REM L33 (12 DUPLICATES REMOVED)
L35	26	S L34 AND PY>1997

L12 ANSWER 1 OF 9 MEDLINE
ACCESSION NUMBER: 2002323162 MEDLINE
DOCUMENT NUMBER: 22061330 PubMed ID: 12065797
TITLE: Preoperative therapy in breast cancer: lessons from the treatment of locally advanced disease.
AUTHOR: Wolff Antonio C; Davidson Nancy E
CORPORATE SOURCE: The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins and The Johns Hopkins University School of Medicine, Baltimore, Maryland 21231-1000, USA.. awolff@jhmi.edu
SOURCE: ONCOLOGIST, **(2002)** 7 (3) 239-45. Ref: 46
Journal code: 9607837. ISSN: 1083-7159.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200207
ENTRY DATE: Entered STN: 20020615
Last Updated on STN: 20020724
Entered Medline: 20020723

AB The greater use of screening has changed the stage distribution of breast cancer, and an increasing number of patients are diagnosed with earlier stages of the disease. Still, locally advanced breast cancer (LABC) remains a major clinical problem in the United States and a common presentation in many parts of the world. There is no standard definition of LABC. One commonly used includes patients with large primary tumors greater than 5 cm (T3) or with skin/chest wall involvement (T4), and/or fixed axillary (N2) or ipsilateral internal mammary (N3) lymph node involvement. According to the tumor node metastasis staging, these usually include stage IIIa (T0-2N2 or T3N1-2) and stage IIIb (T4Nx or TxN3) disease. **Inflammatory breast cancer** (T4d) is included in most classifications despite its distinct clinical behavior and worse prognosis overall, but it serves as an example of combined modality intervention. Historically, the term LABC has been applied to those clinical presentations where the disease is considered inoperable. However, these therapeutic principles (including preoperative or primary systemic therapy [PST]) are increasingly being applied to patients presenting with tumors greater than 5 cm and negative lymph nodes (stage IIb-T3N0) or even smaller tumors, who are considered to have operable disease and a better outcome than those traditionally classified as having LABC. PST is increasingly being used in otherwise operable stage I and II patients aiming at greater rates of breast conservation and earlier efficacy assessment. This article **reviews** many of these issues and ongoing research questions.

L12 ANSWER 2 OF 9 MEDLINE
ACCESSION NUMBER: 2001395944 MEDLINE
DOCUMENT NUMBER: 21229393 PubMed ID: 11328319
TITLE: Congestive heart failure mimicking inflammatory breast carcinoma: a case report and **review** of the literature.
AUTHOR: Oraedu C O; Pinnapureddy P; Alrawi S; Acinapura A J; Raju R
CORPORATE SOURCE: Department of Surgery and Radiology, Lutheran Medical Center, Brooklyn, New York 11220, USA.
SOURCE: Breast J, **(2001 Mar-Apr)** 7 (2) 117-9. Ref: 5
Journal code: 9505539. ISSN: 1075-122X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW OF REPORTED CASES)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010716
Last Updated on STN: 20010716
Entered Medline: 20010712

AB **Inflammatory breast cancer** is a rare but highly malignant form of breast cancer. Biopsy and histologic examination usually confirm the diagnosis. There are rare reports of difficulties in differentiating this particular type of breast malignancy from congestive heart failure (CHF). This difficulty arises when CHF is associated with unilateral breast edema and skin thickening. However, inflammatory breast carcinoma has distinctive histologic and microscopic characteristics allowing the establishment of a proper diagnosis. We report the case of a 65-year-old woman with CHF associated with unilateral breast edema and skin thickening simulating inflammatory breast carcinoma on mammography.

L12 ANSWER 4 OF 9 MEDLINE
ACCESSION NUMBER: 1999270731 MEDLINE
DOCUMENT NUMBER: 99270731 PubMed ID: 10340883
TITLE: Beyond palliative mastectomy in **inflammatory breast cancer**--a reassessment of margin status.
COMMENT: Comment in: Ann Surg Oncol. 1999 Apr-May;6(3):228-9
AUTHOR: Curcio L D; Rupp E; Williams W L; Chu D Z; Clarke K; Odom-Maryon T; Ellenhorn J D; Somlo G; Wagman L D
CORPORATE SOURCE: Department of General Surgery, Keesler Medical Center, Keesler AFB, Mississippi 39534, USA.
SOURCE: ANNALS OF SURGICAL ONCOLOGY, **(1999 Apr-May)** 6 (3) 249-54.
Journal code: 9420840. ISSN: 1068-9265.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199907
ENTRY DATE: Entered STN: 19990715
Last Updated on STN: 19990715
Entered Medline: 19990708

AB BACKGROUND: **Inflammatory breast cancer** is a locally advanced tumor with an aggressive local and systemic course. Treatment of this disease has been evolving over the last several decades. The aim of this study was to assess whether current therapies, both surgical and chemotherapeutic, are providing better local control (LC) and overall survival (OS). We also attempted to identify clinical and pathologic factors that may be associated with improved OS, disease-free survival (DFS), and LC. METHODS: A 25-year retrospective **review** performed at the City of Hope National Medical Center identified 90 patients with the diagnosis of **inflammatory breast cancer**. RESULTS: Of the 90 patients identified with **inflammatory breast cancer**, 33 received neoadjuvant therapy (NEO) consisting of chemotherapy followed by surgery with radiation (n = 26) and without radiation (n = 7). Fifty-seven patients received other therapies (nonNEO). Treatments received by the nonNEO group consisted of chemotherapy, radiation, mastectomy, adrenalectomy, and oophorectomy, alone or in combination. The median follow-up was 28.9 months for the NEO group and 17.6 months for the nonNEO group. Borderline significant differences in the OS distributions between the two groups were found (P = .10), with 3- and 5-year OS for the NEO group of 40.0% and 29.9% and for the nonNEO group of 24.7% and 16.5%, respectively. DFS and LC were comparable in the two groups. Lower stage was associated with an improved OS (P < .05). The 5-year OS for stage IIIB was 30.9%, compared to 7.8% for stage IV. In those patients with stage III disease who were treated with mastectomy and rendered free of disease, margin status was identified by univariate analysis to be a prognostic indicator for OS (P < .05). The 3-year OS, DFS, and LC for patients with negative margins were 47.4%, 37.5%, and 60.3%, respectively, compared to 0%, 16.7%, and 31.3% in patients with positive margins. CONCLUSIONS: This study suggests that in patients with **inflammatory breast cancer** and nonmetastatic disease, an aggressive surgical approach may be justified with the goal of a negative surgical margin. Achievement of this local control is associated with a better overall outcome for this subset of patients. The ability to obtain negative margins may further identify a group of patients with a less aggressive tumor biology that may be more responsive to other modalities of therapy.

L12 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:142574 CAPLUS
DOCUMENT NUMBER: 135:150559
TITLE: Molecular biology of breast cancer metastasis. **Inflammatory breast cancer** : clinical syndrome and molecular determinants
AUTHOR(S): Kleer, Celina G.; van Golen, Kenneth L.; Merajver, Sofia D.
CORPORATE SOURCE: University of Michigan Medical Center, Ann Arbor, MI, USA
SOURCE: Breast Cancer Research [online computer file] (**2000**), 2(6), 423-429
CODEN: BRCRFS; ISSN: 1465-542X
URL: http://breast-cancer-research.com/PDF/bcr-2-6-423.pdf
PUBLISHER: Current Science Ltd.
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
AB A **review** with 49 refs. **Inflammatory breast cancer** (IBC) is an aggressive form of locally advanced breast cancer (LABC) that affects approx. 5% of women with breast cancer annually in the USA. It is a clin. and pathol. distinct form of LABC that is particularly fast growing, invasive, and angiogenic. Nearly all women have lymph node involvement at the time of diagnosis, and approx. 36% have gross distant metastases. Despite recent advances in multimodality treatments, the prognosis of patients with IBC is poor, with a median disease-free survival of less than 2.5 yr. Recent work on the genetic determinants that underlie the IBC phenotype has led to the identification of genes that are involved in the development and progression of this disease. This work has been aided by the establishment of primary human cell lines and animal models. These advances suggest novel targets for future interventions in the diagnosis and treatment of IBC.
REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 2 OF 9 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:354071 BIOSIS
DOCUMENT NUMBER: PREV200200354071
TITLE: Cooperative role of E-**cadherin** and sialyl-Lewis X/A-deficient MUC1 in the passive dissemination of tumor emboli in **inflammatory breast cancer**.
AUTHOR(S): Tomlinson, James S. (1); Kasraeian, Sina (1); Alpaugh, Mary L. (1); Barsky, Sanford H. (1)
CORPORATE SOURCE: (1) Pathology, UCLA School of Medicine, 10833 LeConte Avenue, Los Angeles, CA, 90024 USA
SOURCE: FASEB Journal, (March 20, 2002) Vol. 16, No. 4, pp. A367. http://www.fasebj.org/. print.
Meeting Info.: Annual Meeting of the Professional Research Scientists on Experimental Biology New Orleans, Louisiana, USA April 20-24, 2002
ISSN: 0892-6638.
DOCUMENT TYPE: Conference
LANGUAGE: English

AB Inflammatory breast carcinoma (IBC) is characterized by florid tumor emboli within lymphovascular spaces (LVI). Using a human-scid model of IBC, we have demonstrated that the tumor cell embolus forms on the basis of an overexpressed E-**cadherin**/catenin axis which mediates tumor cell adhesion analogous to the compact embryonic blastocyst. The tumor cell embolus fails to bind endothelial cells because of decreased sialyl-Lewis X/A carbohydrate epitopes on its overexpressed MUC1 which are necessary for binding endothelial cell E-selectin. This tumor-endothelial cell aversion further contributes to the compactness of the embolus and its metastatic passivity. This passivity is manifested by a dramatic increase in pulmonary emboli following palpation of the primary tumor. In assessing this, we compared the effects of palpation of the IBC model with other well known human tumoral xenografts exhibiting no (MCF-7, T47D), low (MDA-MB-231, MDA-MB-468) or high (C8161, M24met) levels of spontaneous metastasis but no LVI. Palpation of each xenograft dramatically increased the numbers and sizes of pulmonary metastases 10-100 fold ($p<.001$) in only the native IBC xenograft. The mechanism of this effect was through a post-palpation release of circulating tumor emboli detected 2-3 minutes after palpation ($p<.01$) by human cytokeratin 19 RT-PCR of murine blood. Our findings support the cooperative role of E-**cadherin** and sialyl-Lewis X/A-deficient MUC1 in passive metastasis of tumor emboli.

L16 ANSWER 4 OF 9 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001254905 MEDLINE
DOCUMENT NUMBER: 21251205 PubMed ID: 11353057
TITLE: Persistent E-**cadherin** expression in **inflammatory breast cancer.**
AUTHOR: Kleer C G; van Golen K L; Braun T; Merajver S D
CORPORATE SOURCE: Department of Pathology, University of Michigan Comprehensive Cancer Center, Ann Arbor, Michigan, USA.. kleer@umich.edu
SOURCE: MODERN PATHOLOGY, (2001 May) 14 (5) 458-64. Journal code: 8806605. ISSN: 0893-3952.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010709
Last Updated on STN: 20010709
Entered Medline: 20010705

AB E-**cadherin** is a transmembrane glycoprotein that mediates epithelial cell-to-cell adhesion. Because loss of E-**cadherin** expression results in disruption of cellular clusters, it has been postulated that E-**cadherin** functions as a tumor suppressor protein. The role of E-**cadherin** in **inflammatory breast cancer** (IBC), a distinct and highly aggressive form of breast cancer, is largely unknown. The aim of our study was to elucidate whether E-**cadherin** expression contributes to the development and progression of the IBC phenotype and to investigate any differences in E-**cadherin** expression between IBC and stage-matched non-IBC. Forty-two breast cancer cases (20 IBC and 22 non-IBC) were identified. Strict and well-accepted criteria were used for the diagnosis of IBC. Clinical and pathologic features were studied, and formalin-fixed, paraffin-embedded tissue sections were immunostained for E-**cadherin**, estrogen and progesterone receptors (ER and PR, respectively), and HER2/neu. Statistical analysis was performed using Fisher's exact test. All IBC uniformly expressed E-**cadherin**, whereas 15 of the 22 (68%) of the non-IBC expressed the protein (P = .006). Intralymphatic tumor emboli in the IBC cases were also all E-**cadherin** positive. Two IBC tumors demonstrated invasive lobular histology, and both cases were positive for E-**cadherin**. Of the non-IBC cases, three were invasive lobular carcinomas, and all were positive for E-**cadherin**. No association was found between E-**cadherin** expression and ER, PR status, or HER2/neu overexpression. Our study demonstrates that there is a strong association between E-**cadherin** expression and IBC and suggests that E-**cadherin** may be involved in the pathogenesis of this form of advanced breast cancer. In our study, we demonstrate that circulating IBC tumor cells strongly express E-**cadherin**, thereby providing an important exception to the positive association between E-**cadherin** loss and poor prognosis in breast cancer.

L29 ANSWER 1 OF 26 MEDLINE
ACCESSION NUMBER: 2000078343 MEDLINE
DOCUMENT NUMBER: 20078343 PubMed ID: 10612219
TITLE: Dose- intensified, preoperative and adjuvant chemotherapy in patients with T3- and T4- breast cancer: toxicity, clinical and pathological remission.
AUTHOR: Blohmer J U; Paepke S; Kissner L; Elling D; Fleige B; Grineisen Y; Lichtenegger W
CORPORATE SOURCE: Klinik fur Frauenheilkunde und Geburtshilfe, Charite Berlin.. jens-u.blohmer@charite.de
SOURCE: ZENTRALBLATT FUR GYNAKOLOGIE, **(1999)** 121 (11) 522-5.
Journal code: 21820100R. ISSN: 0044-4197.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000218
Last Updated on STN: 20000218
Entered Medline: 20000210

AB OBJECTIVE: The aim of the study was to investigate a dose-intensified, preoperative chemotherapy with 3 cycles (cy) of epirubicin 60 mg/m2, ifosfamide 5 g/m2 with mesna 5 g/m2, biweekly with G-CSF 5 micrograms/kg (filgrastim), in terms of toxicity, clinical and pathological remission rates and changes of immunohistochemical characteristics (ER, PR, c-erbB2, **p53**) during chemotherapy of inoperable patients (pt) with poor prognosis (locally advanced (LABC, 9 pt), **inflammatory breast cancer** (IBC, 12 pt) and M0. PATIENTS AND METHODS: Following preoperative chemotherapy (63 cy) and mastectomy patients received adjuvant 3 cy of epirubicin 60 mg/m2 and paclitaxel 175 mg/m2 (biweekly) with G-CSF (54 cy), and subsequently radiation of the thoracic wall and tamoxifen 20 mg/day. RESULTS: Primary toxicity (T): grade 3 alopecia (21 pt), grade 3-4 leucopenia (7 cy), grade 1-2 leucopenia (26 cy), grade 1-2 anemia (61 cy), grade 1-2 neurocortical T (13 cy), grade 1-2 neurosensory T (7 cy), grade 1 cardiac toxicity (1 pt). ORR: 65% (CR: 0 pt, PR: 13 pt, NC: 8 pt). The grades of histological regression were: 0: 14 pt, 1: 6 pt, 2: 0 pt, 3: 1 pt. No significant correlation was observed between the clinical response and the histological regression (Fischer's exact test). The immunohistochemical expression of tumor characteristics did not change significantly during preoperative chemotherapy (Wilcoxon test). 81% of the pt were disease-free after a median follow-up of 20 months (7-26). CONCLUSION: This therapy is safe, feasible and effective, both as primary and adjuvant chemotherapy in women with LABC and IBC.

L29 ANSWER 2 OF 26 MEDLINE
ACCESSION NUMBER: 2000029980 MEDLINE
DOCUMENT NUMBER: 20029980 PubMed ID: 10561251
TITLE: Outcomes of high-dose chemotherapy and autologous stem-cell transplantation in stage IIIB **inflammatory breast cancer.**
AUTHOR: Adkins D; Brown R; Trinkaus K; Maziarz R; Luedke S; Freytes C; Needles B; Wienski D; Fracasso P; Pluard T; Moriconi W; Ryan T; Hoelzer K; Safdar S; Rearden T; Rodriguez G; Khoury H; Vij R; DiPersio J
CORPORATE SOURCE: Division of Bone Marrow Transplantation, Washington University School of Medicine, St Louis, MO 63110-1093, USA.. dadkins@imgate.wustl.edu
SOURCE: JOURNAL OF CLINICAL ONCOLOGY, **(1999 Jul)** 17 (7) 2006-14.
Journal code: 8309333. ISSN: 0732-183X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

(MULTICENTER STUDY)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000616
Last Updated on STN: 20000616
Entered Medline: 20000607

AB PURPOSE: To evaluate the disease-free survival (DFS) and overall survival (OS), prognostic factors, and treatment-related mortality of women with stage IIIB **inflammatory breast cancer** (IBC) treated with combined modality therapy (CMT) and high-dose chemotherapy (HDCT) with autologous stem-cell transplantation. PATIENTS AND METHODS: Between 1989 and 1997, 47 consecutive patients with stage IIIB IBC were treated with CMT and HDCT and were the subject of this retrospective analysis. Chemotherapy was administered to all patients before and/or after definitive surgery. Neoadjuvant and adjuvant chemotherapy was administered to 33 and 34 patients, respectively, and 20 patients received both. All patients received HDCT with autologous stem-cell transplantation, and 41 patients received locoregional radiation therapy. Tamoxifen was prescribed to patients with **estrogen receptor** (ER)-positive cancer. RESULTS: The mean duration of follow-up from diagnosis was 30 months (range, 6 to 91 months) and from HDCT was 22 months (range, 0.5 to 82 months). At 30 months, the Kaplan-Meier estimates of DFS and OS from diagnosis were 57.7% and 59.1%, respectively. At 4 years, the Kaplan-Meier estimates of DFS and OS from diagnosis were 51.3% and 51.7%, respectively. In a multivariate analysis, the only factors associated with better survival were favorable response to neoadjuvant chemotherapy (P =.04) and receipt of tamoxifen (P =.06); however, the benefit of tamoxifen was only demonstrated in patients with ER-positive breast cancer. At last follow-up, 28 patients (59. 6%) were alive and disease-free. Seventeen patients (36.2%) developed recurrent breast cancer. Seventeen patients died: 15 from disease recurrence and two (4.2%) from treatment-related mortality due to HDCT. CONCLUSION: In this analysis, the early results of treatment with CMT and HDCT compare favorably with other series of patients with stage IIIB IBC treated with CMT alone. These outcomes must be confirmed with longer follow-up and controlled studies.

L29 ANSWER 3 OF 26 MEDLINE
ACCESSION NUMBER: 2000005669 MEDLINE
DOCUMENT NUMBER: 20005669 PubMed ID: 10537277
TITLE: A novel human xenograft model of **inflammatory breast cancer.**
AUTHOR: Alpaugh M L; Tomlinson J S; Shao Z M; Barsky S H
CORPORATE SOURCE: Department of Pathology, University of California-Los Angeles School of Medicine, 90024, USA.
SOURCE: CANCER RESEARCH, **(1999 Oct 15)** 59 (20) 5079-84.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199911
ENTRY DATE: Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991110

AB The step of intravasation or lymphovascular invasion can be a rate-limiting step in the metastatic process. Inflammatory breast carcinoma manifests an exaggerated degree of lymphovascular invasion in situ; hence, a study of its molecular basis might shed light on the general mechanism of lymphovascular invasion exhibited by all metastasizing cancers. To this end, we have established the first human transplantable inflammatory breast carcinoma xenograft (MARY-X) in scid/nude mice. Whereas all other human xenografts grew as isolated s.c.

nodules, MARY-X grew exclusively within murine lymphatics and blood vessels, and these latter elements and their supporting stroma comprised, by murine Cot-1 DNA analysis, 30% of the tumor. MARY-X, like its human counterpart, exhibited striking erythema of the overlying skin. MARY-X was estrogen receptor, progesterone receptor, Her-2/neu negative and **p53**, epidermal growth factor receptor positive. The primary tumor of origin of MARY-X exhibited identical markers, except that about 50% of its cells exhibited Her-2/neu amplification. Comparative studies of MARY-X with noninflammatory xenografts indicated 10-20-fold overexpression of E-cadherin and MUC1, findings that were reflected in actual cases of human **inflammatory breast cancer**. MARY-X should allow us to further dissect out both the upstream regulatory machinery and the downstream effector molecules responsible for the inflammatory carcinoma phenotype.

L29 ANSWER 4 OF 26 MEDLINE
ACCESSION NUMBER: 1998342404 MEDLINE
DOCUMENT NUMBER: 98342404 PubMed ID: 9677440
TITLE: Age as a prognostic factor in breast cancer.
AUTHOR: Vanlemmens L; Hebbar M; Peyrat J P; Bonneterre J
CORPORATE SOURCE: Centre Oscar Lambret (Northern France Cancer Centre), Lille, France.
SOURCE: ANTICANCER RESEARCH, **(1998 May-Jun)** 18 (3B) 1891-6.
Journal code: 8102988. ISSN: 0250-7005.
PUB. COUNTRY: Greece
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199807
ENTRY DATE: Entered STN: 19980817
Last Updated on STN: 19980817
Entered Medline: 19980731

AB We retrospectively analysed data from 1751 patients with non-metastatic and non-**inflammatory breast cancer** treated in our institution between 1977 and 1989, in order to evaluate the link between age and prognosis in breast cancer. We chose three age groups (1): < or = 33 (n = 67), 34-40 (n = 155), > 40 years (n = 1529). There were no significant differences in the distribution of clinical tumor size (T), histological node status (N), histology of the primary-tumor and **progesterone receptor** levels (PR). Younger patients had a higher proportion of SBR III ($p < 0.0001$), and of Estradiol Receptor negative tumors (EP). There was a significant difference between the three groups in terms of overall survival ($p < 0.035$), breast cancer specific survival ($p < 0.0001$) and relapse-free survival ($p < 0.0002$). Younger patients had a significantly poorer prognosis (survival and relapse) than older ones. Multivariate analysis of specific survival demonstrated that young age at diagnosis was a poor independent prognostic factor.

L29 ANSWER 5 OF 26 MEDLINE
ACCESSION NUMBER: 1998338546 MEDLINE
DOCUMENT NUMBER: 98338546 PubMed ID: 9673758
TITLE: **Inflammatory breast cancer:** enhanced local control with hyperfractionated radiotherapy and infusional vincristine, ifosfamide and epirubicin.
AUTHOR: Gurney H; Harnett P; Kefford R; Boyages J
CORPORATE SOURCE: Department of Medical Oncology and Palliative Care, Westmead Hospital, Sydney, NSW.
SOURCE: AUSTRALIAN AND NEW ZEALAND JOURNAL OF MEDICINE, **(1998 Jun)** 28 (3) 400-2.
Journal code: 1264322. ISSN: 0004-8291.
PUB. COUNTRY: Australia
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 199810
ENTRY DATE: Entered STN: 19981021
Last Updated on STN: 19981021
Entered Medline: 19981015

AB Local control rate for **inflammatory breast cancer** (IBC) is < 50% with standard chemotherapy-radiotherapy regimen. Nineteen women (age range 40-65, median 50 years) with IBC (18 patients) or with a primary tumour of > 10 cm (one patient) received a novel treatment comprising hyperfractionated radiotherapy (HFRT) sandwiched between two cycles of infusional chemotherapy using vincristine, ifosfamide and epirubicin (VIE). The primary endpoint was local control. VIE was continuously infused for six weeks via a Hickman's line using a Deltec CADD-1 ambulatory pump. Ifosfamide (3 gm/m2) mixed with equi-dose mesna was infused for seven days and alternated every week with an infusion of epirubicin (50 mg/m2) mixed with vincristine (1.5 mg/m2). HFRT consisted of 1.5 Gy twice daily for 34 frct (51 Gy) followed by a boost of 15 Gy in 10 frct. The total treatment time was less than 22 weeks. Median follow-up was 37 months. Local control rate was 58%. Three patients failed to respond initially and five relapsed in the breast at a median time of 36.8 months. Median overall and disease-free survival was 18 and 25.3 months respectively. Toxicity from VIE was minimal (WHO gd 3 emesis--two patients, gd 3 mucositis--one patient, neutropenic sepsis--three patients). Radiotherapy caused moist desquamation in 17/19 patients. Twenty-four central lines were complicated by seven line infections, three thromboses, and one extravasation. The local control rate of 58% with VIE + HFRT appears similar to reported chemoradiotherapy regimen, although the treatment time of 22 weeks is **much** shorter than other regimens which take up to 12 months. Toxicity is acceptable. Hickman-related complications need to be reduced. The study is ongoing.

L29 ANSWER 6 OF 26 MEDLINE
ACCESSION NUMBER: 1998293936 MEDLINE
DOCUMENT NUMBER: 98293936 PubMed ID: 9632147
TITLE: Inflammatory breast carcinoma: a community hospital experience.
AUTHOR: Brooks H L; Mandava N; Pizzi W F; Shah S
CORPORATE SOURCE: Department of Surgery, Cornell University Medical College, St. John's Queens Hospital, Catholic Medical Center of Brooklyn and Queens, Jamaica, Queens, NY 11432, USA.
SOURCE: JOURNAL OF THE AMERICAN COLLEGE OF SURGEONS, **(1998 Jun)** 186 (6) 622-9.
Journal code: 9431305. ISSN: 1072-7515.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199806
ENTRY DATE: Entered STN: 19980708
Last Updated on STN: 19980708
Entered Medline: 19980625

AB BACKGROUND: **Inflammatory breast cancer** (IBC) is a rare form of rapidly progressive breast cancer. We reviewed the diagnosis, treatment, and outcome of IBC in our inner city community-based hospital and compared results with previous published reports. STUDY DESIGN: Twenty-five patients were diagnosed and treated for IBC at the Catholic Medical Center of Brooklyn and Queens during the 6-year period of January 1989 through December 1995. Criteria for inclusion in this study were clinical or histopathologic evidence, or both, of inflammatory carcinoma. RESULTS: IBC comprised 2.0% (25 of 1,257) of all breast cancer patients initially diagnosed during this study. All presented with clinical signs of IBC. Invasion of dermal lymphatics by neoplastic cells was demonstrated in 68% (17 of 25) of biopsy specimens. Sixty-eight percent (17 of 25) of patients presented with metastatic (ie, stage IV)

disease and 28% (7 of 25) with stage IIIb; one patient (4%) died before staging. Estrogen and **progesterone receptor** studies were done on 72% (18 of 25) of all specimens. Of those patients who died, 85% were estrogen and **progesterone receptor** negative; of those surviving, 60% were **estrogen receptor** positive. Twenty (80%) of the 25 patients died, after a mean survival of 11.8 months and 5 (20%) remain alive, with a mean survival of 44.8 months. Of those who died, 85% were stage IV at presentation. All five survivors were stage IIIb at presentation. Patients underwent a variety of multimodal therapies. Survival was significantly associated with earlier stage at diagnosis and **estrogen receptor** positivity. CONCLUSIONS: IBC is characterized by rapid progression and dismal outcome. Earlier stage at diagnosis and positive **estrogen receptor** status suggest a more favorable prognosis. Neoadjuvant chemotherapy, as part of a multimodal approach, has significantly improved the outcome for IBC, but this is limited to patients with stage IIIb disease. Most of our patients presented with stage IV disease. If improvement is to be realized at the community level, limited health care resources must be directed toward aggressive physician and public education.

L29 ANSWER 7 OF 26 MEDLINE
ACCESSION NUMBER: 1998246288 MEDLINE
DOCUMENT NUMBER: 98246288 PubMed ID: 9586876
TITLE: High-dose chemotherapy with autologous hematopoietic progenitor-cell support as part of combined modality therapy in patients with **inflammatory breast cancer.**
AUTHOR: Cagnoni P J; Nieto Y; Shpall E J; Bearman S I; Baron A E; Ross M; Matthes S; Dunbar S E; Jones R B
CORPORATE SOURCE: Bone Marrow Transplant Program and Department of Preventive Medicine and Biometrics, University of Colorado Health Sciences Center, Denver 80262, USA..
pcagnoni@entente.uhcolorado.edu
SOURCE: JOURNAL OF CLINICAL ONCOLOGY, **(1998 May)** 16 (5) 1661-8.
Journal code: 8309333. ISSN: 0732-183X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199806
ENTRY DATE: Entered STN: 19980611
Last Updated on STN: 19980611
Entered Medline: 19980604

AB PURPOSE: To evaluate the feasibility of high-dose chemotherapy (HDC) with autologous hematopoietic progenitor-cell support (AHPCS) as part of combined modality therapy (CMT) in patients with **inflammatory breast cancer** (IBC). PATIENTS AND METHODS: From April 1993 to March 1997, 30 patients with IBC were treated at our program. Twenty-three patients received neoadjuvant chemotherapy (NAC) before HDC; 18 patients also received adjuvant chemotherapy following surgery, but before HDC. All patients received HDC with high-dose cyclophosphamide, cisplatin, and carmustine (BCNU) with AHPCS. Every patient underwent surgery either before (27 patients) or after (three patients) HDC. Patients received radiotherapy after HDC in addition to tamoxifen if their tumors were **estrogen receptor**-positive. RESULTS: Thirteen patients experienced grade 3 or 4 nonhematologic noninfectious toxicities. In 12 patients (40%), this represented drug-induced lung injury, which in all cases responded to a 10-week course of corticosteroids. The only treatment-related death was secondary to hemolytic-uremic syndrome (HUS). Another patient suffered grade 4 CNS toxicity, which was completely reversible. All patients engrafted promptly. Eight patients relapsed, five of whom had a poor pathologic

response to NAC. Relapses were local (five patients), local plus systemic (one), or systemic only (two). Median follow-up time from diagnosis and HDC is 23.5 (range, 7 to 49) and 19 (range, 4 to 44) months, respectively. Twenty-one patients (70%; 95% confidence interval [CI], 51% to 86%) remain alive and free of disease 4 to 44 months after HDC. Median disease-free survival (DFS) and overall survival have not yet been reached. CONCLUSION: HDC as part of CMT is feasible in patients with IBC. The toxicity of this treatment program is significant, but tolerable. Despite the short follow-up duration, the promising DFS observed in this group of patients warrants randomized studies that include a HDC-containing arm in patients with IBC.

L29 ANSWER 8 OF 26 MEDLINE
ACCESSION NUMBER: 1998052438 MEDLINE
DOCUMENT NUMBER: 98052438 PubMed ID: 9392545
TITLE: Original **p53** status predicts for pathological response in locally advanced breast cancer patients treated preoperatively with continuous infusion 5-fluorouracil and radiation therapy.
AUTHOR: Formenti S C; Dunnington G; Uzieli B; Lenz H; Keren-Rosenberg S; Silberman H; Spicer D; Denk M; Leichman G; Groshen S; Watkins K; Muggia F; Florentine B; Press M; Danenberg K; Danenberg P
CORPORATE SOURCE: Department of Radiation Oncology, University of Southern California School of Medicine, Los Angeles 90033, USA.
CONTRACT NUMBER: 1ROI CA 60859-01A1 (NCI)
CA 14089 (NCI)
SOURCE: INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY, BIOLOGY, PHYSICS, **(1997 Dec 1)** 39 (5) 1059-68.
Journal code: 7603616. ISSN: 0360-3016.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199712
ENTRY DATE: Entered STN: 19980109
Last Updated on STN: 19980109
Entered Medline: 19971211

AB PURPOSE/OBJECTIVE: 1) To test feasibility of preoperative continuous infusion (c.i.) 5-Fluorouracil (5-FU) and radiation (RT) in locally advanced breast cancer. 2) To study clinical and pathological response rates of 5-FU and radiation. 3) To attempt preliminary correlations between biological probes and pathological response. METHODS AND MATERIALS: Previously untreated, locally advanced breast cancer patients were eligible: only patients who presented with T3/T4 tumors that could not be resected with primary wound closure were eligible, while **inflammatory breast cancer** patients were excluded. The protocol consisted of preoperative c.i. infusion 5-FU, 200 mg/m2/day with radiotherapy, 50 Gy at 2 Gy fractions to the breast and regional nodes. At mastectomy, pathological findings were classified based on persistence of invasive cancer: pathological complete response (pCR) = no residual invasive cells in the breast and axillary contents; pathological partial response (pPR) = presence of microscopic foci of invasive cells in either the breast or nodal specimens; no pathological response (pNR) = pathological persistence of tumor. For each patient pretreatment breast cancer biopsies were analyzed by immunohistochemistry for nuclear grade, ER/PR hormonal receptors, her2/neu and **p53** overexpression. RESULTS: Thirty-five women have completed the protocol and are available for analysis. 5-FU was interrupted during radiation in 10 of 35 patients because of oral mucositis in 8 patients, cellulitis in 1, and patient choice in another. Objective clinical response rate before mastectomy was 71% (25 of 35 patients): 4 CR, 21 PR. However, in all 35 patients tumor response was sufficient to make them resectable with primary wound closure. Accordingly, all patients underwent modified

radical mastectomy: primary wound closure was achieved in all patients. At mastectomy there were 7 pCR (20%), 5 pPR (14%) and the remaining 23 patients (66%) had pathological persistence of cancer (pNR). Variables analyzed as potential predictors for pathological response (pPR and pCR) were: initial TNM clinical stage, clinical response, nuclear grade, hormonal receptor status, **p53** overexpression, and Her2/neu overexpression in the pretreatment tumor biopsy. Only initial **p53** status (lack of overexpression at immunohistochemistry) significantly correlated with achievement of a pathological response to this regimen (p = 0.010). CONCLUSION: The combination of c.i. 5-FU and radiation was well tolerated and generated objective clinical responses in 71% of the patients. With the limitation of the small sample size, the complete pathological response achieved (20%) compares favorably with that reported in other series of neoadjuvant therapy for similar stage breast cancer. These preliminary data suggest that initial **p53** status predicts for pathological response (pPR and pCR) to the combination of c.i. 5-FU and radiotherapy in locally advanced breast cancer.

L29 ANSWER 9 OF 26 MEDLINE
ACCESSION NUMBER: 96309999 MEDLINE
DOCUMENT NUMBER: 96309999 PubMed ID: 8732652
TITLE: Metaplastic breast carcinoma: a cytohistologic and clinical study of 10 cases.
AUTHOR: Johnson T L; Kini S R
CORPORATE SOURCE: Department of Pathology, Henry Ford Hospital, Detroit, MI 48202, USA.
SOURCE: DIAGNOSTIC CYTOPATHOLOGY, **(1996 May)** 14 (3) 226-32. Ref: 15
Journal code: 8506895. ISSN: 8755-1039.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, MULTICASE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199610
ENTRY DATE: Entered STN: 19961025
Last Updated on STN: 19961025
Entered Medline: 19961016

AB Metaplastic breast carcinomas (MBC) account for < 5% of breast malignancies and have an uncertain prognostic significance. The tumors tend to grow rapidly, and most are negative for hormone receptors. Adenosquamous carcinomas and various types of carcinosarcomas may be classified as MBC. We evaluated the cytologic, histologic, and clinical parameters of 10 MBC to determine important diagnostic features of these tumors. A cytologic diagnosis of MBC, based on the identification of two distinct malignant components, was made preoperatively in five of 10 (50%) cases, and retrospectively in two additional cases; two specimens were inadequately cellular. Poorly-differentiated adenocarcinoma was the most frequently encountered component of MBC. It is recommended that malignant breast aspirates be carefully scrutinized for multiple neoplastic components. Our series of MBC differs from previous reports in that two cases presented as **inflammatory breast cancer**, one case was pregnancy-associated, and there was a higher incidence of estrogen and **progesterone receptor** positivity. No cancer-related deaths occurred during a mean follow-up period of over 6 yr.

L29 ANSWER 10 OF 26 MEDLINE
ACCESSION NUMBER: 94373421 MEDLINE
DOCUMENT NUMBER: 94373421 PubMed ID: 7916250
TITLE: High-dose chemotherapy with autologous stem cell support for breast cancer: a review of the Dana-Farber Cancer Institute/Beth Israel Hospital experience.

AUTHOR: Ayash L J; Elias A; Wheeler C; Tepler I; Schwartz G; Schnipper L; Frei E; Antman K
CORPORATE SOURCE: Dana-Farber Cancer Institute, Beth Israel Hospital, Harvard Medical School, Boston, MA 02115.
SOURCE: JOURNAL OF HEMATOTHERAPY, **(1993 Winter)** 2 (4) 507-11. Ref: 8
Journal code: 9306048. ISSN: 1061-6128.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, MULTICASE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199410
ENTRY DATE: Entered STN: 19941031
Last Updated on STN: 19950206
Entered Medline: 19941014

AB The overall median survival of women with advanced or high-risk primary breast cancer has not changed with conventional chemotherapy. Regimens employing high-dose chemotherapy with autologous stem cell support (ABMT) have been developed with the hope of optimizing tumor response and increasing survival. Early phase I studies in women with advanced refractory disease achieved high response rates of short duration. Second generation studies combined an induction phase followed by one high-dose intensification at time of maximum tumor response. The Dana-Farber Cancer Institute/Beth Israel Hospitals have developed the high-dose intensification regimen of cyclophosphamide, thiotepa, and carboplatin (CTCb) for use in women with metastatic and high-risk stage IIIB/ **inflammatory breast cancer**. To date, approximately 19% of women with metastatic disease remain progression free using this approach, with median length of follow-up approaching 40 months. Although the median duration of follow-up for the stage IIIB women is **much** shorter (approximately 12 months), greater than 90% of these women are thus far disease free. With the advent of hematologic support, such as blood stem cells and colony-stimulating factors, the morbidity, mortality, and costs associated with this treatment have been substantially reduced, allowing for two or more cycles of high-dose intensification to be employed, to exploit the potential of dose-intensity to optimize response.

L29 ANSWER 11 OF 26 MEDLINE
ACCESSION NUMBER: 94071623 MEDLINE
DOCUMENT NUMBER: 94071623 PubMed ID: 8250712
TITLE: Images of **estrogen-receptor**-positive breast tumors produced by estradiol labeled with iodine I 123 at 16 alpha.
AUTHOR: Kenady D E; Pavlik E J; Nelson K; van Nagell J R; Gallion H; DePriest P D; Ryo U Y; Baranczuk R J
CORPORATE SOURCE: Department of Surgery, University of Kentucky College of Medicine, Lexington.
CONTRACT NUMBER: HD-16087 (NICHD)
SOURCE: ARCHIVES OF SURGERY, **(1993 Dec)** 128 (12) 1373-81.
Journal code: 9716528. ISSN: 0004-0010.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199401
ENTRY DATE: Entered STN: 19940201
Last Updated on STN: 19970203
Entered Medline: 19940106

AB OBJECTIVE: To examine the suitability of estradiol labeled with iodine I 123 at 16 alpha for imaging **estrogen-receptor**-positive breast carcinoma using imaging instrumentation that is widely available.

DESIGN: Single-photon emission computed tomographic imaging survey of 29 women with suspected primary or expected recurrent breast carcinoma. SETTING: University-based referral center. PARTICIPANTS: Twenty-nine women undergoing diagnosis for primary or recurrent breast carcinoma. Selection was voluntary. MAIN OUTCOME MEASURE: Qualitative imaging study designed to provide tomographic data of radioligand retention and descriptive data of imaging results. RESULTS: Single-photon emission computed tomographic imaging using 123I-estradiol at 16 alpha was performed for patients with breast carcinoma. Independent readers, without knowledge of receptor status or proven disease, interpreted the films. Scintigraphic detection was most noteworthy in patients with chest wall tumors and **inflammatory breast cancer**. Agreement between readers was 98% for true-negative readings and 94% for true-positive readings, but only 60% for false-positive and false-negative film readings. CONCLUSIONS: Our results indicated that areas shown on imaging were also found to have **estrogen-receptor** activity and that radioligand accumulation can occur with low frequency in some surgically explored tissue. Radioligand imaging with 16 alpha-123I-estradiol can locate **estrogen-receptor** -positive breast tumors, including some that may be difficult to detect using conventional diagnostic imaging.

L29 ANSWER 12 OF 26 MEDLINE
ACCESSION NUMBER: 92357811 MEDLINE
DOCUMENT NUMBER: 92357811 PubMed ID: 1353891
TITLE: Two distinct mechanisms alter **p53** in breast cancer: mutation and nuclear exclusion.
AUTHOR: Moll U M; Riou G; Levine A J
CORPORATE SOURCE: Department of Molecular Biology, Lewis Thomas Laboratory, Princeton University, NJ 08544-1014.
CONTRACT NUMBER: CA37656 (NCI)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, **(1992 Aug 1)** 89 (15) 7262-6.
Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199209
ENTRY DATE: Entered STN: 19920925
Last Updated on STN: 20000303
Entered Medline: 19920904

AB Twenty-seven cases of **inflammatory breast cancer** were screened for the presence of the **p53** protein by immunocytochemical methods using a monoclonal antibody directed against the **p53** protein. Three groups were detected: 8 cases (30%) had high levels of **p53** in the nucleus of the cancer cells; 9 cases (33%) had a complete lack of detectable staining; 10 cases (37%) showed a pattern of cytoplasmic staining with nuclear sparing. Nucleotide sequence analysis of **p53** cDNAs derived from the samples with cytoplasmic staining revealed only wild-type **p53** alleles in 6 out of 7 cases. An eighth case was determined to be wild type by a single-strand conformation polymorphism. In contrast, the samples containing nuclear **p53** contained a variety of missense mutations and a nonsense mutation. The **p53** cDNAs from 3 of the tumors that lacked detectable **p53** staining were analyzed, and all 3 had wild-type nucleotide sequences. Interestingly, a case of normal lactating breast tissue also showed intense cytoplasmic staining for **p53** with nuclear sparing. These data suggest that some breast cancers that contain the wild-type form of **p53** protein may inactivate its tumor-suppressing activity by sequestering this protein in the cytoplasm, away from its site of action in the cell nucleus. The detection of cytoplasmic **p53** in normal lactating breast tissue could suggest

that this is the mechanism employed in specific physiological situations to permit transient cell proliferation. This observation could explain how some breast cancer tissues inactivate **p53** function without mutation.

L29 ANSWER 13 OF 26 MEDLINE
ACCESSION NUMBER: 91086967 MEDLINE
DOCUMENT NUMBER: 91086967 PubMed ID: 1985172
TITLE: How American oncologists treat breast cancer: an assessment of the influence of clinical trials.
AUTHOR: Belanger D; Moore M; Tannock I
CORPORATE SOURCE: Department of Medicine, Princess Margaret Hospital, Toronto, Ontario, Canada.
SOURCE: JOURNAL OF CLINICAL ONCOLOGY, **(1991 Jan)** 9 (1) 7-16.
Journal code: 8309333. ISSN: 0732-183X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199102
ENTRY DATE: Entered STN: 19910322
Last Updated on STN: 19910322
Entered Medline: 19910207

AB The present study was designed to assess the preferred methods of treatment of breast cancer by American oncologists, and the impact of clinical trials on their practice. We mailed 465 questionnaires to surgical, radiation, or medical oncologists. The questionnaire described five hypothetic patients with breast cancer, and respondents were asked to select their preferred treatment for each patient. For primary breast cancer, most physicians would offer the choice of local excision followed by radiation therapy or modified radical mastectomy. About 80% of physicians would prescribe adjuvant chemotherapy for a premenopausal woman with **estrogen receptor**-negative, axillary node negative breast cancer, and for a postmenopausal woman with **estrogen receptor**-negative, node-positive disease. This policy was favored by male and female physicians of each specialty. Almost all respondents would treat a young woman with **inflammatory breast cancer** with initial chemotherapy followed by radiation and/or surgery, and about 60% would recommend chemotherapy to a postmenopausal patient with **estrogen receptor**-negative disease and minimally symptomatic bone metastases. Clinical trials have compared treatment strategies that could be applied to patients described in our questionnaire. Preferred treatments for primary breast cancer, and for **inflammatory breast cancer** are supported by the results of clinical trials. Recommendation of adjuvant chemotherapy for node-negative breast cancer is not based on a consistent demonstration of improvement in survival, although randomized trials with short follow-up have shown delay to recurrence. Recommendation of adjuvant chemotherapy for a postmenopausal woman with node-positive breast cancer is contrary to the results of large randomized controlled trials (and to a meta-analysis), which have shown that this policy does not lead to improved survival. Our report suggests that even large randomized clinical trials may have a minimal impact on practice if their results run counter to belief in the value of the treatment.

L29 ANSWER 14 OF 26 MEDLINE
ACCESSION NUMBER: 91068881 MEDLINE
DOCUMENT NUMBER: 91068881 PubMed ID: 2252134
TITLE: Multimodal therapy in locally advanced breast carcinoma.
AUTHOR: Lopez M J; Andriole D P; Kraybill W G; Khojasteh A
CORPORATE SOURCE: Department of Surgery, Washington University School of Medicine, Barnes Hospital, St. Louis, Missouri 63110.
SOURCE: AMERICAN JOURNAL OF SURGERY, **(1990 Dec)** 160 (6)

669-74; discussion 674-5.
Journal code: 0370473. ISSN: 0002-9610.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199101
ENTRY DATE: Entered STN: 19910308
Last Updated on STN: 19910308
Entered Medline: 19910115

AB Among 879 patients treated for breast cancer between 1975 and 1984, advanced disease was found in 125 (14%). A subgroup of 34 (4%) presented with untreated locally advanced disease without demonstrable distant metastases at the time of diagnosis (stage IIIB = T4abed, NX-2,MO). During the first 5 years (1975 through 1979), 17 patients were treated primarily with sequential radiotherapy and chemotherapy (Group A). From 1980 to 1984 (Group B), the management consisted of four courses of induction multi-drug chemotherapy followed primarily by mastectomy and additional chemotherapy. The mean follow-up for the most recent group (Group B) is 48 months. Follow-up was complete. While the local disease control rate was the same for both groups (76%), the survival was remarkably different. Group A patients experienced a median survival of 15 months, and only one survived 5 years. In Group B, the median survival was 56 months with nine patients (53%) alive between 40 and 76 months, seven (41%) of whom are 5-year survivors. While the overall mortality of patients with **inflammatory breast cancer** was greater in both groups when compared with the group with noninflammatory disease, the survival of patients in Group B was better than in Group A for both inflammatory and noninflammatory cancers (p less than 0.01). **Estrogen receptor**, nodal, and menopausal status did not influence survival. These data suggest that neoadjuvant chemotherapy improves survival for patients with stage IIIB breast carcinoma and delays the establishment or progression of distant metastases. Mastectomy is an important component in the treatment of this disease.

L29 ANSWER 15 OF 26 MEDLINE
ACCESSION NUMBER: 90381673 MEDLINE
DOCUMENT NUMBER: 90381673 PubMed ID: 2205369
TITLE: Comprehensive management of locally advanced breast cancer.
AUTHOR: Hortobagyi G N
CORPORATE SOURCE: Department of Medical Oncology, University of Texas, M.D. Anderson Cancer Center, Houston 77030.
SOURCE: CANCER, **(1990 Sep 15)** 66 (6 Suppl) 1387-91. Ref: 49
Journal code: 0374236. ISSN: 0008-543X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199010
ENTRY DATE: Entered STN: 19901122
Last Updated on STN: 19901122
Entered Medline: 19901019

AB The definition of locally advanced breast cancer includes patients with large tumors, extensive regional lymph node involvement, or direct involvement of the skin or underlying chest wall. Most of these patients have very poor survival with standard treatment modalities, and over the past 20 years combined modality therapy has been used to improve local and systemic control. There is limited information suggesting that patients with operable locally advanced breast cancer have an improved survival if treated with surgery (or radiation therapy) followed by systemic chemotherapy, as compared with patients treated with local modalities

alone. Uncontrolled trials strongly suggest that patients with any stage of locally advanced breast cancer achieve high response rates after induction chemotherapy. Most of these patients can be rendered disease free after combined modality therapy, and their disease-free and overall survival rates appear to be improved when compared with historical controls. These results are most impressive for patients with **inflammatory breast cancer**, a disease previously found to be uniformly lethal when treated with local modalities of therapy alone. More recently, 30% to 50% of these patients were alive and disease free 5 years after diagnosis, and a substantial percentage were in the same condition 10 years later. Combined modality therapies are the most appropriate approach to patients with locally advanced breast cancer. **Much** additional research must be done to improve the results of these therapies and maximize the survival of patients with locally advanced breast cancer.

L29 ANSWER 16 OF 26 MEDLINE
ACCESSION NUMBER: 90373447 MEDLINE
DOCUMENT NUMBER: 90373447 PubMed ID: 3079407
TITLE: Breast cancer.
AUTHOR: Loprinzi C L; Carbone P P
SOURCE: CANCER CHEMOTHERAPY AND BIOLOGICAL RESPONSE MODIFIERS, **(1987)** 9 338-57. Ref: 195
Journal code: 8812385. ISSN: 0921-4410.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199010
ENTRY DATE: Entered STN: 19901122
Last Updated on STN: 19901122
Entered Medline: 19901012

AB This year, manuscripts addressed numerous pertinent breast cancer issues. Notable conclusions from each of the discussed sections suggest that: (a) oral contraceptives do not increase a woman's risk for breast cancer; (b) the vast majority of women with resected premalignant breast lesions do well for prolonged periods after diagnosis regardless of therapy; (c) satisfactory cosmetic results can occur with either lumpectomy, axillary nodal dissection, and radiotherapy or with mastectomy and breast reconstruction; (d) the primary tumor thymidine labeling index can give prognostic information; (e) immunohistochemical methods can accurately measure tumor **estrogen receptors**; (f) there are multiple hormonal therapies of similar efficacy; (g) two new single agent chemotherapy drugs deserving further investigation are idarubicin and lonidamine; (h) none of several combination chemotherapy regimens is clearly superior to any of the other 'standard' regimens; (i) there is a lack of consensus among the conclusions of recent adjuvant breast cancer consensus conferences held in the United States and London; (j) **inflammatory breast cancer** patients treated with initial combination chemotherapy consistently appear to have improved relapse-free and overall survivals when compared to historical controls; and (k) the prognosis in locally recurrent breast cancer patients is better in those previously treated with lumpectomy and irradiation when compared to those previously treated with mastectomy.

L29 ANSWER 17 OF 26 MEDLINE
ACCESSION NUMBER: 90206600 MEDLINE
DOCUMENT NUMBER: 90206600 PubMed ID: 2181374
TITLE: Strong association between c-myb and oestrogen-receptor expression in human breast cancer.
AUTHOR: Guerin M; Sheng Z M; Andrieu N; Riou G
CORPORATE SOURCE: Laboratoire de Pharmacologie Clinique et Moleculaire,

Institut Gustave Roussy, Villejuif, France.
SOURCE: ONCOGENE, **(1990 Jan)** 5 (1) 131-5.
Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199005
ENTRY DATE: Entered STN: 19900601
Last Updated on STN: 20000303
Entered Medline: 19900504

AB Previous articles have reported that the c-myb proto-oncogene was activated in various types of tumours of the hematopoietic system suggesting that this gene plays a role in the development of these malignancies. However no studies of the c-myb gene have as yet been performed in solid primary tumours. In the present study we have analysed in breast cancer the c-myb gene with the aim to determine its involvement in tumour progression. Expression of the c-myb oncogene was analysed from 169 carcinoma specimens obtained from untreated patients with non-**inflammatory breast cancer** (NBC) (112 patients) and **inflammatory breast cancer** (IBC) (57 patients). A 3.5 kb c-myb transcript band was detected in 108 (64%) tumours. c-myb expression was found to be associated with good prognostic factors (lowest histopathologic grade (P = 0.01), oestrogen and **progesterone receptor** status (P less than 10(-4)) and pS2 gene expression (P less than 10(-4)) and negatively correlated with breast cancers of poorer prognosis, namely IBC (P = 0.03) and NBC with multiple involved nodes (P = 0.15). Other genes (c-myc, c-erbB2, c-fos and epidermal growth factor receptor) were also studied. The c-myb gene expression was found to be inversely correlated (P less than 0.03) with only c-erbB2 overexpression in NBC. When data were analysed with a logistic regression model using a stepwise procedure, c-myb expression was found to be associated only with the oestrogen receptor status (P less than 10(-4)). In conclusion, our data indicate that analysis of c-myb expression in breast cancer could allow the characterization of a new class of oestrogen-dependent tumours.

L29 ANSWER 18 OF 26 MEDLINE
ACCESSION NUMBER: 89138699 MEDLINE
DOCUMENT NUMBER: 89138699 PubMed ID: 2563719
TITLE: Structure and expression of c-erbB-2 and EGF receptor genes in inflammatory and non-**inflammatory breast cancer**: prognostic significance.
AUTHOR: Guerin M; Gabillot M; Mathieu M C; Travagli J P; Spielmann M; Andrieu N; Riou G
CORPORATE SOURCE: Laboratoire de Pharmacologie Clinique et Moleculaire, INSERM U287, Institut Gustave Roussy, Villejuif, France.
SOURCE: INTERNATIONAL JOURNAL OF CANCER, **(1989 Feb 15)** 43 (2) 201-8.
Journal code: 0042124. ISSN: 0020-7136.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198903
ENTRY DATE: Entered STN: 19900306
Last Updated on STN: 20000303
Entered Medline: 19890327

AB C-erbB-2 and epidermal growth factor receptor (**EGFR**) genes were independently shown to be associated with breast cancer progression. In this report, we have analyzed the structure and expression of these 2 genes in the same tumor specimens of a large series of breast cancers. Two clinical types of tumor were studied: inflammatory (IBC) and non-**inflammatory breast cancers** (NBC) obtained

from 221 untreated patients at different clinical stages. Amplification and over-expression of the c-erbB-2 proto-oncogene were observed in 27% and 47% of tumors, respectively, and were strongly associated with breast cancers of the most unfavorable prognosis, namely IBC and NBC with multiple positive axillary nodes. **EGFR** gene was neither amplified nor rearranged. A restriction fragment length polymorphism (RFLP) for HindIII endonuclease was observed. **EGFR** transcripts were detected in 46% of tumors and observed more frequently in IBC than in NBC (p less than 0.02). In NBC the presence of **EGFR** transcripts increased linearly with lymph-node involvement and was associated with estrogen-receptor-negative tumors (p = 0.01). Analysis of both genes from the same tumor samples indicated that genes are associated with cancer aggressiveness. Furthermore, in NBC these 2 genes were independently activated, in contrast to IBC in which activated genes were negatively correlated, suggesting that c-erbB-2 and **EGFR** genes play different roles in NBC and IBC.

L29 ANSWER 19 OF 26 MEDLINE
ACCESSION NUMBER: 86090565 MEDLINE
DOCUMENT NUMBER: 86090565 PubMed ID: 4079435
TITLE: Inflammatory breast carcinoma: a distinct entity?.
AUTHOR: Kokal W A; Hill L R; Porudominsky D; Beatty J D; Kemeny M M; Riihimaki D U; Terz J J
SOURCE: JOURNAL OF SURGICAL ONCOLOGY, **(1985 Nov)** 30 (3) 152-5.
Journal code: 0222643. ISSN: 0022-4790.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198602
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19900321
Entered Medline: 19860211

AB Sixty-four patients with the diagnosis of either inflammatory or locally advanced breast cancer were analyzed with respect to age, menopausal status, **estrogen receptor** protein (ERP) measurements, characteristics on clinical presentation, disease-free interval (DFI), and overall survival. There were no significant differences between the two groups in the patients' clinical presentation, DFI, or overall survival time. Patients with inflammatory carcinoma were significantly younger as well as more likely to be pre- or perimenopausal than patients with locally advanced breast cancer. Of those patients who had ERP measurements performed, patients with **inflammatory breast cancer** had a significantly decreased incidence of ERP(+) tumors in comparison to patients with locally advanced breast cancer. These results suggest that inflammatory carcinoma of the breast behaves as an ERP(-) subtype of locally advanced breast carcinoma rather than a truly distinct entity.

L29 ANSWER 20 OF 26 MEDLINE
ACCESSION NUMBER: 83283858 MEDLINE
DOCUMENT NUMBER: 83283858 PubMed ID: 6309290
TITLE: [**Inflammatory breast cancers**: correlation between anatomopathology and steroid receptor assay].
Les cancers du sein inflammatoires: correlation entre anatomopathologie et dosage des recepteurs steroidiens.
AUTHOR: Mauriac L; Wafflart J; Trojani M; Durand M
SOURCE: BULLETIN DU CANCER, **(1983)** 70 (3) 160-4.
Journal code: 0072416. ISSN: 0007-4551.
PUB. COUNTRY: France
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: French

FILE SEGMENT: Priority Journals
ENTRY MONTH: 198310
ENTRY DATE: Entered STN: 19900319
Last Updated on STN: 19980206
Entered Medline: 19831008

AB From a series of 89 clinically **inflammatory breast cancers**, the authors settle a subgroup of tumors, the infiltrative ductal carcinomas with a pleomorphic structure. They have better histological and hormonal prognostic criteria than the other carcinomas, especially the infiltrative ductal carcinomas with an atypical structure: lower SBR grading (p = 6.10(-5)), estrogen and **progesterone receptors** positive rate more frequently (p = 10(-4)). A prospective study will allow to confirm the better response to treatment and especially the better survival rate of this metastatic high risk breast cancer subgroup.

L29 ANSWER 21 OF 26 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:811957 CAPLUS
DOCUMENT NUMBER: 132:235144
TITLE: Expression of epidermal growth factor receptor in breast cancer, from early stages to advanced disease
AUTHOR(S): Neskovic-Konstantinovic, Z.; Nikolic-Vukosavljevic, D.; Brankovic-Magic, M.; Kanjer, K.; Gavrilovic, D.; Mitrovic, L.; Borojevic, N.; Vukotic, Dj.; Spuzic, I.
CORPORATE SOURCE: Dept. Medical Oncology, Belgrade, Yugoslavia
SOURCE: Journal of Experimental & Clinical Cancer Research (**1999**), 18(3), 347-355
CODEN: JECRDN; ISSN: 0392-9078
PUBLISHER: Regina Elena Institute for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Epidermal growth factor receptor was detd. in 106 newly diagnosed breast cancer patients, using the biochem. method. The group consisted of 58 patients in stage I-II, and 48 patients in stage III-IV. Although a significant inverse correlation was found between EGF-R status, and ER or PR status, quant. content of EGF-R did not correlate either with quant. ER, or PR levels. The ER/PR content was similar in all clin. stages, suggesting their stability during the clin. course of the disease. EGF-R content was significantly higher in stage IV, compared to stage I, while intermediate clin. stages and all substages did not differ according to the EGF-R content. EGF-R was confirmed as a weak prognostic factor within clin. stages. However, in a whole group, the overall survival was significantly better in patients whose tumors EGF-R content was lower than 26 fmol/mg, compared to those with higher ERF-R content. EGF-R content was highly predictive for the response to systemic endocrine treatment, in metastatic breast cancer patients. In locally advanced breast cancer a trend towards higher levels of EGF-R was found in **inflammatory breast cancers**, compared to non-inflammatory ones.
Slightly higher levels were found in responders to local non-endocrine primary treatments (radiotherapy with or without chemotherapy), compared to non-responders, suggesting the possible predictive role of EGF-R for the response to such treatments. Our results emphasized the usefulness of quant. receptor detn. suggesting the relative stability of EGF-R content during the clin. course of breast cancer, its independence from ER, its significant predictive and weak prognostic values, and a possible correlation with the aggressiveness of the disease, and response to non-endocrine treatments.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 22 OF 26 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:93252 BIOSIS
DOCUMENT NUMBER: PREV199900093252
TITLE: Survival after autologous hematopoietic stem cell

transplantation for patients with inflammatory breast carcinoma.
AUTHOR(S): Arun, Banu; Slack, Rebecca; Gehan, Edmund; Spitzer, Thomas; Meehan, Kenneth R. (1)
CORPORATE SOURCE: (1) Div. Hematol. and Oncol., Bone Marrow Transplant Program, Georgetown Univ. Med. Cent., 3800 Reservoir Road N.W., Washington, DC 20007 USA
SOURCE: Cancer, (**Jan. 1, 1999**) Vol. 85, No. 1, pp. 93-99. ISSN: 0008-543X.
DOCUMENT TYPE: Article
LANGUAGE: English
AB BACKGROUND. The authors retrospectively determined the clinical outcome of patients with inflammatory breast carcinoma (IBC) treated with high dose chemotherapy (HDC) and autologous bone marrow (ABM) or peripheral blood stem cell (PBSC) support. METHODS. Twenty-four consecutive patients with IBC received HDC, including escalating doses of carboplatin (range, 1.2-1.8 g/m2) and cyclophosphamide (range, 4.8-6.0 g/m2) over 3 days followed by ABM (n = 5) or PBSC infusion (n = 19). Restaging evaluation was performed 100 days after transplant, every 6 months for 2 years, and then yearly thereafter. After transplantation, fifteen patients received immunotherapy with interleukin-2 (IL-2) or IL-2 and interferon-alpha. RESULTS. The 2-year estimated disease free survival (DFS) and overall survival (OS) for these patients were 71% (90% confidence interval (CI), 55-87%) and 73% (90% CI, 53-93%), respectively. The median follow-up of surviving patients was 19 months (range, 8-68 months). Six patients developed disease recurrence at a median of 10 months (range 4-16 months) after transplantation. Four of these 6 patients died from metastatic disease at a median of 18 months (range, 14-21 months). Using the generalized Wilcoxon test and the Cox proportional hazards regression model, patients with tumors that demonstrated **estrogen receptors** had an improved DFS (P = 0.03). CONCLUSIONS. Combining liDC and ABM or PBSC for patients with IBC may yield an improved OS and DFS.

L29 ANSWER 23 OF 26 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1996:477118 BIOSIS
DOCUMENT NUMBER: PREV199699206674
TITLE: Breast cancer in patients under 18 years. Report of an inflammatory case and review of the literature.
AUTHOR(S): Louvet, C.; Espie, M. (1); De Rocquancourt, A.; Schaison, G.; Extra, J. M.; Marty, M.
CORPORATE SOURCE: (1) Serv. d'Oncologie Medicale, Hopital Saint-Louis, 1 avenue Claude Vellefaux, 75010 Paris France
SOURCE: Breast, (1996) Vol. 5, No. 4, pp. 277-281. ISSN: 0960-9776.
DOCUMENT TYPE: Article
LANGUAGE: English
AB We report a case of **inflammatory breast cancer** in an 11-year-old girl. She was treated with chemotherapy, surgery and radiotherapy, followed by intensification and autologous bone marrow transplantation. She relapsed 8 months after the end of treatment and died 2 months later with polymetastatic disease. Genetic studies did not identify any mutation of the **p53** gene. Sixty-four cases of breast cancer in patients under 18 years have been reported. Thirty-eight were sufficiently described to be discussed. In two-thirds of patients, pathologic examination showed a secretory juvenile carcinoma. Prognosis in this group was good with only one death reported. In the other patients, poorly differentiated or inflammatory carcinomas were described. Mortality in this group is high. Well differentiated carcinoma were reported in two patients. Paediatric breast cancer appears to be different from the adult disease with regard to history, sex ratio and prognosis. Therapeutic implications are discussed.

L29 ANSWER 24 OF 26 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1996:198642 BIOSIS
DOCUMENT NUMBER: PREV199698754771
TITLE: Prognostic factors predicting outcome in high risk stage II, III and **inflammatory breast cancer** patients undergoing high dose chemotherapy followed by autologous stem cell rescue.
AUTHOR(S): Bazzini, M. D.; Fields, K. K.; Elfenbein, G. J.; Perkins, J. B.; Kronish, L. E.; Janssen, W. E.
CORPORATE SOURCE: Moffitt Cancer Cent., Univ. South Fla., Tampa, FL 33612 USA
SOURCE: Breast Cancer Research and Treatment, (1996) Vol. 37, No. SUPPL., pp. 54.
Meeting Info.: 18th Annual San Antonio Breast Cancer Symposium San Antonio, Texas, USA December 8-13, 1995
ISSN: 0167-6806.
DOCUMENT TYPE: Conference
LANGUAGE: English

L29 ANSWER 25 OF 26 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1990:71532 BIOSIS
DOCUMENT NUMBER: BA89:39358
TITLE: GENETIC ALTERATIONS OF C-MYC C-ERBB-2 AND C-HA-RAS PROTOONCOGENES AND CLINICAL ASSOCIATIONS IN HUMAN BREAST CARCINOMAS.
AUTHOR(S): CARCIA I; DIETRICH P-Y; AAPRO M; VAUTHIER G; VADAS L; ENGEL E
CORPORATE SOURCE: DIV. ONCOHEMATOL., UNIV. HOSP., FAC. MED., 1211 GENEVA, SWITZERLAND.
SOURCE: CANCER RES, (1989) 49 (23), 6675-6679.
CODEN: CNREA8. ISSN: 0008-5472.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB We have analyzed genomic DNA sequences from 125 prospectively collected single unilateral primary breast carcinoma samples for the presence of alterations of c-myc, c-erbB-1, c-erbB-2, c-Ki-ras and c-Ha-ras protooncogenes. Amplification of the c-myc gene was found in 18% of the samples, and in one sample a non-germ line c-myc related DNA fragment or rearrangement was detected. We have found a significant association (P = 0.0010) between amplified c-myc gene and inflammatory carcinoma, a particularly aggressive breast cancer. The c-erbB-2 gene was amplified in 22% of the tumor samples and a rearrangement was observed once. Alteration of the c-erbB-2 gene was significantly linked to histological grade III tumors (P = 0.0005) and the absence of estrogen and **progesterone receptors** (P = 0.036). No amplifications were observed for c-erbB-1, c-Ki-ras, and c-Ha-ras genes. About 40% of breast carcinomas contain either amplified c-myc or c-erbB-2 protooncogenes, whereas simultaneous amplification of both was seen in only one sample, suggesting the involvement of two distinct molecular mechanisms in breast cancer. Comparison of DNA from peripheral blood and tumor samples indicated loss of one c-Ha-ras allele in 29% of patients heterozygous for this polymorphism. A significant correlation (P = 0.016) between c-Ha-ras locus (11p14) allele loss and patient survival was found. These data suggest that 11p14 allelic loss plays a role in the evolution of human breast cancer, amplification of c-erbB-2 gene is associated with increasing stage of malignancy, and alteration of the c-myc gene in inflammatory breast carcinoma may contribute to the rapid progression of this human tumor subtype.

L29 ANSWER 26 OF 26 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 95066196 EMBASE
DOCUMENT NUMBER: 1995066196
TITLE: Biological and clinical relevance of proliferative activity in **inflammatory breast cancer**
.
AUTHOR: Paradiso A.; Mangia A.; Tortora G.; Schittulli F.; De Lena

M.
CORPORATE SOURCE: Experimental/Applied Oncology Lab., Oncology Institute, Via Amendola 209,Bari 70126, Italy
SOURCE: International Journal of Oncology, (1995) 6/3 (563-567). ISSN: 1019-6439 CODEN: IJONES
COUNTRY: Greece
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The hormone receptor status and proliferative activity characteristics of **inflammatory breast cancer** (IBC) were studied in a series of 46 patients. ER and PgR were measured by the DCC method and proliferative activity was by the 3H-thymidine autoradiographic labeling index (3H-Tdr-LI). Tumors were ER and PgR positive in 42% and 38% of cases, respectively, whereas median 3H-Tdr-LI was 3.8%. With regard to clinical aspects, overall survival (OS) was not affected by either ER status (36 cases) or 3H-Tdr-LI value (33 cases). On the contrary, PgR+ status was able to individualize women with a significantly higher probability of OS (X2 by long rank test, p = 0.03) after 35 months of follow-up. In the subgroup of 14 patients subjected to double biopsy performed before and after administration of primary polychemotherapy, the tumor proliferative activity variations were not related to clinical outcome.

=> d his

(FILE 'HOME' ENTERED AT 12:58:12 ON 23 SEP 2002)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE' ENTERED AT 12:58:34 ON 23 SEP 2002

L1	792	S INFLAMMAT### BREAST CANCER
L2	29	S L1 (P) XENOGRAFT
L3	10	DUP REM L2 (19 DUPLICATES REMOVED)
L4	249147	S BREAST CANCER
L5	2022	S L4 (P) XENOGRAFT
L6	1201	S L4 (10A) INFLAMMAT###
L7	29	S L6 (P) XENOGRAFT
L8	10	DUP REM L7 (19 DUPLICATES REMOVED)
L9	10	DUP REM L3 L8 (10 DUPLICATES REMOVED)
L10	79	S L1 AND REVIEW
L11	49	DUP REM L10 (30 DUPLICATES REMOVED)
L12	9	S L11 AND PY>1998
L13	0	S L11 AND ?CADHERIN
L14	17	S L1 AND ##CADHERIN
L15	0	S L11 AND ##CADHERIN
L16	9	DUP REM L14 (8 DUPLICATES REMOVED)
L17	26	S L1 AND P53
L18	11	DUP REM L17 (15 DUPLICATES REMOVED)
L19	7	S L1 AND EGFR
L20	4	DUP REM L19 (3 DUPLICATES REMOVED)
L21	13	DUP REM L18 L20 (2 DUPLICATES REMOVED)
L22	17	S L1 AND MUC#
L23	17	S L1 AND MUC##
L24	8	DUP REM L23 (9 DUPLICATES REMOVED)
L25	19	DUP REM L21 L24 (2 DUPLICATES REMOVED)
L26	79	S L1 AND (ESTROGEN RECEPTOR OR PROGESTERONE RECEPTOR)
L27	38	DUP REM L26 (41 DUPLICATES REMOVED)
L28	48	DUP REM L25 L27 (9 DUPLICATES REMOVED)
L29	26	S L28 AND PY<2000

L35 ANSWER 1 OF 26 MEDLINE
ACCESSION NUMBER: 2001184265 MEDLINE
DOCUMENT NUMBER: 21147836 PubMed ID: 11250604
TITLE: [Preclinical evaluation of aromatase inhibitors antitumor activity].
Evaluation preclinique del'activite antitumorale des inhibiteurs de l'aromatase.
AUTHOR: Auvray P; Bichat F; Genne P
CORPORATE SOURCE: Oncodesign Biotechnology, Parc technologique de la Toison-d'Or, 28, rue de Broglie, 21000 Dijon, France.
SOURCE: BULLETIN DU CANCER, **(2000 Dec)** 87 Spec No 7-22.
Ref: 179
Journal code: 0072416. ISSN: 0007-4551.
PUB. COUNTRY: France
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW LITERATURE)
LANGUAGE: French
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010329

AB Aromatase is an enzymatic complex responsible for the conversion of androgens into estrogens; these hormones are important in development, reproduction, but also in the growth of estrogen-dependent cancer. This enzyme is present in 60-70% of the **breast cancer**. The aromatase inhibitors are important drugs in the **breast cancer** treatment of postmenopausal women. In order to study their in vivo activity, **animal models** have been developed, e.g. **rat** with tumour induced by 7,12-dimethylbenz[a]anthracene, PMSG-primed immature **rat** or athymic nude **mice** with aromatase transfected MCF-7 **xenograft**. In this **review**, we were interested in preclinical results obtained with both classes: steroidal and nonsteroidal inhibitors. The former group, as substrate analogs formestane or exemestane, are irreversible, selective and long-lasting inhibitors of aromatase. The nonsteroidal molecules, such as letrozole or anastrozole, are reversible inhibitors with high affinity. Finally, knowledge of the enzyme active site, with molecular modeling and site-directed mutagenesis, could be useful to develop new inhibitor families, more specific and potent in vivo.

L35 ANSWER 2 OF 26 MEDLINE
ACCESSION NUMBER: 1999249545 MEDLINE
DOCUMENT NUMBER: 99249545 PubMed ID: 10235466
TITLE: Novel anticancer drugs in Japan.
AUTHOR: Ogawa M
CORPORATE SOURCE: Aichi Cancer Center, Nagoya, Japan.
SOURCE: JOURNAL OF CANCER RESEARCH AND CLINICAL ONCOLOGY, **(1999)** 125 (3-4) 134-40. Ref: 29
Journal code: 7902060. ISSN: 0171-5216.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990614
Last Updated on STN: 19990614
Entered Medline: 19990601

AB This **review** summarizes the results reported in preclinical and clinical trials of three novel anticancer drugs developed and tested in Japan. In phase II trials, Irinotecan, a semisynthetic analog of

camptothecin, has yielded response rates exceeding 20% in non-small-cell lung cancer, small-cell lung cancer, **breast cancer**, gastric cancer, colorectal cancer, ovarian cancer, uterine cervical cancer, and non-Hodgkini's lymphoma. It was modestly active on pancreatic cancer and was not active on acute leukemias. Dose-limiting toxicities were leukopenia and diarrhea, and other major toxicities were nausea, vomiting, and alopecia. Amrubicin, a totally synthetic anthracycline, exhibited both higher efficacy on human tumor **xenografts** and cardiotoxicity milder than that of doxorubicin in preclinical studies. The dose-limiting toxicity in phase I trials was leukopenia. In phase II trials, amrubicin has shown activity equivalent to that of doxorubicin on non-Hodgkin's lymphoma, response rates exceeding 20% on non-small-cell lung cancer, and a response rate of 78.8% on untreated extensive-stage small-cell lung cancer. S-1 is an oral formulation consisting of ftorafur (an analog of 5-fluorouracil), 5-chloro-2, 4-dehydropyrimidine, which inhibits degradation of 5-fluorouracil, and potassium oxonate, which reduces gastrointestinal toxicity, at a molar ratio of 1:0.4:1. In phase I trials, dose-limiting toxicities (myelosuppression and gastrointestinal toxicities) were judged to be milder than those induced by UFT (ftorafur plus uracil). The response rates obtained in phase II trials were 40-49% on advanced gastric cancer, 35.5% on colorectal cancer, 37.5% on head and neck cancer, and 40.7% on **breast cancer**.

L35 ANSWER 3 OF 26 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:429802 CAPLUS
DOCUMENT NUMBER: 137:41199
TITLE: Trastuzumab in the treatment of HER2 positive **breast cancer**
AUTHOR(S): Summerhayes, Maxwell
CORPORATE SOURCE: The Pharmacy Department, Guy's Hospital, London, SE1 9RT, UK
SOURCE: Journal of Oncology Pharmacy Practice (**2001**), 7(1), 9-25
CODEN: JOPPFI; ISSN: 1078-1552
PUBLISHER: Arnold, Hodder Headline
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A **review**. The aim of this study was to provide a comprehensive **review** of the preclin. and clin. pharmacol. and toxicol. of the monoclonal antibody trastuzumab, with particular ref. to its use in its approved indication, HER2/neu-overexpressing **breast cancer**. A MEDLINE search was conducted using the terms "trastuzumab" and "Herceptin" for the period 1995-2001. The ref. lists from retrieved articles were reviewed and other relevant papers identified. The abstr. books from the annual meetings of the American Society of Clin. and Oncol. and the European Society of Medical Oncol. were also reviewed. The aim of the **review** was to be comprehensive and descriptive. All studies contg. information deemed to be of interest were reviewed by the author; none were excluded on grounds of quality. Trastuzumab is a chimeric monoclonal antibody with a hypervariable region of murine origin inserted into a human IgG1 skeleton. Trastuzumab recognizes p185HER2/neu, the 185-kDa product of the HER2/neu protooncogene. This gene is overexpressed in around 20% of **breast cancers** and encodes for a transmembrane protein that has extensive structural homol. with the EGFR. HER2/neu overexpression is prognostic of short relapse-free and overall survival and, possibly, of poor response to certain hormonal and cytotoxic treatments. Trastuzumab inhibits the growth of HER2/neu-overexpressing tumor cells grown in tissue culture or as **xenografts** in **mice**. It also potentiates the action of certain cytotoxic drugs against such cells. These properties stimulated clin. trials of trastuzumab in women with HER2/neu-pos. **breast cancer**. Used alone, in women with heavily pretreated HER2/neu-pos. **breast cancer**, trastuzumab stabilized disease in 35% of cases and induced regression in a further

22%. Its use was assocd. with prolonged stabilization of quality of life. When used in combination with paclitaxel, or anthracycline-based chemotherapy, as a first-line treatment for metastatic **breast cancer**, it increased response rates, time to disease progression and survival. Unfortunately, when used in conjunction with anthracyclines, trastuzumab has been assocd. with an unacceptable incidence of cardiotoxicity. For this reason, it is currently approved for use alone or in combination with paclitaxel. When added to paclitaxel as a first-line treatment, it increased the median time to disease progression from 3.0 to 6.9 mo (P=0.0001) and the 1-yr survival rate from 62% to 73%, with little toxicity except occasional and, generally, mild infusion reactions.

REFERENCE COUNT: 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 4 OF 26 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2002:184182 CAPLUS

DOCUMENT NUMBER: 137:18320

TITLE: The role of mitogen-activated protein (MAP) kinase in **breast cancer**

AUTHOR(S): Santen, Richard J.; Song, Robert Xinde; McPherson, Robert; Kumar, Rakesh; Adam, Liana; Jeng, Meei-Huey; Yue, Wei

CORPORATE SOURCE: Division of Endocrinology, Department of Medicine, University of Virginia Health System, Charlottesville, VA, 22908, USA

SOURCE: Journal of Steroid Biochemistry and Molecular Biology (**2002**), 80(2), 239-256
CODEN: JSBBEZ; ISSN: 0960-0760

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A **review**. Mitogen-activated protein kinase (MAP kinase) cascades transmit and amplify signals involved in cell proliferation as well as cell death. These signal transduction pathways serve as an indicators of the intensity of trafficking induced by various growth factor, steroid hormone, and G protein receptor mediated ligands. Three major MAP kinase pathways exist in human tissues, but the one involving ERK-1 and -2 is most relevant to **breast cancer**.
Peptide growth factors acting through tyrosine kinase contg. receptors are the major regulators of ERK-1 and -2. Estradiol, progesterone, and testosterone can act non-genomically via membrane assocd. receptors to activate MAP kinase as can various other ligands acting through heterotrimeric G protein receptors. Recent studies demonstrate that **breast cancers** frequently contain an increased proportion of cells with the activated form of MAP kinase. In estrogen receptor pos. breast tumors, MAP kinase pathways can exert "cross talk" effects at the level of ER induced transcription as well as at the level of the cell cycle. Estradiol stimulates cell proliferation by mechanisms which involve activation of MAP kinase, either through rapid, non-transcription effects or by increasing growth factor prodn. and consequently MAP kinase. Progesterone and androgens also stimulate MAP kinase through both of these two mechanisms. Strategies used to treat hormone dependent **breast cancer** appear to result in upregulation of MAP kinase activation. Direct exptl. data demonstrate that the pressure of estradiol deprivation results in the upregulation of MAP kinase in **breast cancer** cells growing in tissue culture and as **xenografts**. A no. of investigators have now studied the expression of activated MAP kinase in human **breast cancer** tissues by enzymic assay and by immunohistochem. techniques. Approx. half of breast tumors express more activated MAP kinase than does the surrounding benign tissue. Studies show a trend toward higher MAP kinase activity in primary tumors of node pos. than in node neg. patients. However, larger nos. of patients must be studied for

these results to achieve statistical significance. The up-regulation of MAP kinase activity does not represent mutations of Ras, but appears to result from enhancement of growth factor pathway activation. No data are yet available on the relationship between MAP kinase activation and apoptosis. Addnl. studies are now needed to det. the precise relationship between MAP kinase activation and tumor proliferation, apoptosis, and degree of invasiveness as well as on disease free and overall survival.
REFERENCE COUNT: 125 THERE ARE 125 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 5 OF 26 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:141692 CAPLUS
DOCUMENT NUMBER: 137:76608
TITLE: Malignant cells, directors of the malignant process: Role of transforming growth factor-beta
AUTHOR(S): Teicher, Beverly A.
CORPORATE SOURCE: Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN, USA
SOURCE: Cancer and Metastasis Reviews (**2001**), 20(1/2), 133-143
CODEN: CMRED4; ISSN: 0167-7659
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A **review**. Malignant cells survive and thrive by expressing growth and invasion "programs" that many normal cell types recognize and respond to in "programmed" patterns. An early event in the mol. evolution of many malignancies loss of response to growth control by transforming growth factor-beta (TGF-.beta.) frequently due to mutation in the type I or type II TGF-.beta. receptor or a Smad protein. The malignant cells secrete TFG-.beta. that acts on the host to suppress antitumor immune responses, to enhance extracellular matrix prodn. and to augment angiogenesis. These activities resemble those induced by TGF-.beta. during embryonic development and account in part for the "de-differentiated" nature of malignant disease. Clin., TGF-.beta.1 is often elevated in the plasma of **breast cancer** patients, lung cancer patients, hepatocellular carcinoma patients, and prostate cancer patients. Preclinically, several **breast cancer** models and prostate cancer models in vivo have demonstrated a connection between TGF-.beta. expression and increased tumorigenicity, increased invasion and drug resistance. In other diseases such as colon, gastric, endometrial, ovarian, and cervical cancers and gliomas and melanoma, loss of response to TGF-.beta. as a growth inhibitor and increased expression of TGF-.beta. have been assocd. with malignant conversion and progression. Elevated levels of TGF-.beta. are measurable in nude **mice** bearing a wide variety of human tumor **xenografts**; thus, these tumor models may serve as useful mimics of the human disease with respect to the TGF-.beta. pathway. Cancer cure may be approached by blocking several of the major normal pathways used for tumor growth and survival in combination with cytotoxic therapies.
REFERENCE COUNT: 180 THERE ARE 180 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 6 OF 26 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:53817 CAPLUS
DOCUMENT NUMBER: 137:118875
TITLE: Inhibition of erbB receptor (HER) tyrosine kinases as a strategy to abrogate antiestrogen resistance in human **breast cancer**
AUTHOR(S): Kurokawa, Hirokazu; Arteaga, Carlos L.
CORPORATE SOURCE: Departments of Medicine and Cancer Biology and Vanderbilt-Ingram Cancer Center, Vanderbilt University

School of Medicine, Nashville, TN, 37232, USA
SOURCE: Clinical Cancer Research (**2001**), 7(12, Suppl.), 4436S-4442S
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A **review**. It has been proposed that binding of ligand to the estrogen receptor (ER) releases its assocn. with transcriptional corepressors, allowing the ER to recruit coactivators, which possess histone acetylase activity, and induce transcription of gene promoters contg. estrogen response elements. It has also been proposed that the antiestrogen tamoxifen recruits transcriptional corepressors to the AF-2 region of the hormone-binding domain of the ER, thus blocking ER-mediated transcription. The ER cross-talks with a no. of mitogenic signaling pathways and second messengers, like the epidermal growth factor receptor, the insulin-like growth factor-1 receptor, mitogen-activated protein (MAP) kinase, phosphatidylinositol-3 kinase/Akt, dopamine, and cAMP. Some of these mols. may: (a) support ligand-independent ER transcription; (b) increase the assocn. of ER with coactivators of transcription; and/or (c) reduce the antiestrogen-induced assocn. of ER with corepressors. These events either alone or in combination may result in hormone independence and/or antiestrogen resistance. The authors have examd. whether signaling by HER2/neu (erbB-2) receptor tyrosine kinase, which can induce antiestrogen resistance, can also disrupt the tamoxifen-induced interaction of ER with transcriptional corepressors. Notably, tamoxifen-induced assocn. of ER with the transcriptional corepressors N-CoR or SMRT was reduced in HER2-overexpressing breast tumor cells but not in cells with low HER2 levels. Small mol. inhibitors of the HER2 kinase or MAP extracellular signal-regulated kinase 1/2 or dominant-neg. MAP extracellular signal-regulated kinase 1/2 constructs restored the inhibitory effect of tamoxifen on both ER-mediated transcription and tumor cell proliferation. Treatment with both tamoxifen and the small mol. HER1/2 kinase inhibitor AG1478 reduced mitogen-activated protein kinase activity and markedly reduced growth of established MCF-7/HER2 **xenografts** in athymic nude **mice**. Similar results have been obtained with ZD1839 ("Iressa"), an epidermal growth factor receptor (HER1) tyrosine kinase inhibitor. Taken together, these data suggest that exogenous inhibitors of the HER-signaling network and other mitogenic pathways can abrogate or delay the emergence of antiestrogen resistance, thus providing an evaluable therapeutic strategy in human breast carcinoma.
REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 7 OF 26 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:834925 CAPLUS
DOCUMENT NUMBER: 137:41103
TITLE: Studies of epidermal growth factor receptor inhibition in **breast cancer**
AUTHOR(S): Bundred, N. J.; Chan, K.; Anderson, N. G.
CORPORATE SOURCE: Academic Department of Surgery, University Hospital of South Manchester, Manchester, M20 8LR, UK
SOURCE: Endocrine-Related Cancer (**2001**), 8(3), 183-189
CODEN: ERCAE9; ISSN: 1351-0088
PUBLISHER: Society for Endocrinology
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A **review**. Until recently, there has been little knowledge on the growth control of estrogen receptor (ER)-neg. ductal carcinoma in situ (DCIS) and invasive **breast cancer**. The recent development of DCIS models, such as transgenic **mice**, cell-line **xenograft** models and, importantly, in vivo human DCIS

xenograft models has facilitated the investigation and understanding of the control of growth of early pre-invasive breast lesions. Recent studies have shown that ER-neg. DCIS, unlike ER-pos. DCIS, is hormone independent and does not respond to anti-estrogen treatment. Moreover, DCIS of the comedo type utilizes type I tyrosine kinase growth factors, such as epidermal growth factor receptor (EGFR) and c-erbB-2, in receptor signaling for growth. New data underscore the importance of EGFR as the major modulating growth factor receptor in the control of proliferation in the breast. Pre-clin. studies performed on human DCIS **xenografts** in nude **mice** suggest a potential role for EGFR tyrosine kinase inhibitors (EGFR-TKIs). More specifically, ZD1839, a novel orally active and selective EGFR-TKI, has been shown to produce a response in DCIS through a decrease in epithelial proliferation. These findings have enhanced our knowledge of signal transduction pathways in cancer and indicate that tyrosine kinase blockade of EGFR has potential for the treatment and chemoprevention of DCIS. It is hoped that further advances in this area and evaluation of EGFR-TKIs in Phase II/III clin. trials will allow their therapeutic potential as anticancer agents to be appreciated.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 8 OF 26 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:515663 CAPLUS
DOCUMENT NUMBER: 135:313639
TITLE: DHEA and Its Transformation into Androgens and Estrogens in Peripheral Target Tissues: Intracrinology
AUTHOR(S): Labrie, Fernand; Luu-The, Van; Labrie, Claude; Simard, Jacques
CORPORATE SOURCE: Oncology and Molecular Endocrinology Research Center, Laval University Medical Center (CHUL), and Laval University, Quebec, G1V 4G2, Can.
SOURCE: Frontiers in Neuroendocrinology (**2001**), 22(3), 185-212
CODEN: FNEDA7; ISSN: 0091-3022
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A **review**, with refs. A new understanding of the endocrinol. of menopause is that women, at menopause, are not only lacking estrogens resulting from cessation of ovarian activity but have also been progressively deprived for a few years of androgens and some estrogens originating from adrenal DHEA and androstenedione (4-dione). In fact, serum DHEA decreases by about 60% between the maximal levels seen at 30 yr of age to the age of menopause. This decreased secretion of DHEA and DHEA-S by the adrenals is responsible for a parallel decrease in androgen and estrogen formation in peripheral tissues by the steroidogenic enzymes specifically expressed in each cell type in individual target tissues. This new field of endocrinol., called intracrinol., describes the local synthesis of androgens and estrogens made locally in each cell of each peripheral tissue from the adrenal precursors DHEA and 4-dione. These androgens and estrogens exert their action in the same cells where their synthesis takes place and they are released from these target cells only after being inactivated. To further understand the effect of DHEA in women, DHEA has been administered in postmenopausal women for 12 mo. Such treatment resulted in increased bone formation and higher bone mineral d. accompanied by elevated levels of osteocalcin, a marker of bone formation. Vaginal maturation was stimulated, while no effect was obsd. on the endometrium. Preclin. studies, on the other hand, have shown that, due to its predominant conversion into androgens, DHEA prevents the development and inhibits the growth of dimethylbenz(a)anthracene-induced mammary carcinoma in the **rat**, a model of **breast cancer** . DHEA also inhibits the growth of human **breast cancer** ZR-75-1 **xenografts** in nude **mice**. The inhibitory

effect of DHEA on **breast cancer** is due to an androgenic effect of testosterone and dihydrotestosterone made locally from DHEA. When used as replacement therapy, DHEA is free of the potential risk of breast and uterine cancer, while it stimulates bone formation and vaginal maturation and decreases insulin resistance. The combination of DHEA with a fourth generation SERM, such as EM-652 (SCH 57068), a compd. having pure and potent antiestrogenic activity in the mammary gland and endometrium, could provide major benefits for women at menopause (inhibition of bone loss and serum cholesterol levels) with the assocd. major advantages of preventing breast and uterine cancer. A widely used application of intracrinol. is the treatment of prostate cancer where the testicles are blocked by an LHRH agonist while the androgens made locally in the prostate from DHEA are blocked by a pure antiandrogen. Such treatment, called combined androgen blockade, has led to the first demonstration of a prolongation of life in prostate cancer. (c) 2001 Academic Press.

REFERENCE COUNT: 106 THERE ARE 106 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 9 OF 26 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:788988 CAPLUS
DOCUMENT NUMBER: 134:81010
TITLE: EM-652 (SCH 57068), a third generation SERM (selective estrogen receptor modulator), acting as pure antiestrogen in the mammary gland and endometrium
AUTHOR(S): Labrie, Claude; Labrie, Fernand; Belanger, Alain; Simard, Jacques; Luo, Shouqi; Martel, Celine
CORPORATE SOURCE: Oncology and Molecular Endocrinology Research Center, Laval University Medical Center (CHUL) and Laval University, Quebec, QC, G1V 4G2, Can.
SOURCE: International Congress Series (**2000**), 1206(Current Knowledge in Reproductive Medicine), 381-397
CODEN: EXMDA4; ISSN: 0531-5131
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A **review** with 92 refs. Estrogens are well recognized to play the predominant role in **breast cancer** development and growth and much efforts have been devoted to the blockade of estrogen formation and action. The most widely used therapy of **breast cancer** which has shown benefits at all stages of the disease is the use of the antiestrogen Tamoxifen. This compd., however, possesses mixed agonist and antagonist activities and major efforts have thus been devoted to the development of compds. having pure antiestrogenic activity in the mammary gland and endometrium. Such a compd. would avoid the problem of stimulation of the endometrium and the risk of endometrial carcinoma. The authors have thus synthesized an orally active nonsteroidal antiestrogen, EM-652 (SCH 57068) and the prodrug EM-800 (SCH 57050) which are the most potent of the known antiestrogens. EM-800, the prodrug of EM-652, has been shown to prevent the development of dimethylbenz(a)anthracene (DMBA)-induced mammary carcinoma in the **rat**, a well-recognized model of human **breast cancer**. Not only the development, but also the growth of established DMBA-induced mammary carcinoma was inhibited by treatment with EM-800. Uterine size was reduced to castration levels in the groups of **animals** treated with EM-800. EM-652 was the most potent antiestrogen to inhibit the growth of human **breast cancer** ZR-75-1, MCF-7 and T-47D cells in vitro when compared with ICI 182780, ICI 164384, hydroxytamoxifen, raloxifene, and Droloxifene. Moreover, EM-652 and EM-800 have no stimulatory effect on the basal levels of cell proliferation in the absence of E2 while hydroxytamoxifen, raloxifene, and Droloxifene have a stimulatory effect on the basal growth

of T-47D and ZR-75-1 cells. When human **breast cancer** ZR-75-1 **xenografts** were grown in nude **mice**, EM-800 led to a complete inhibition of the stimulatory effect of estrogens in ovariectomized **mice** while tamoxifen was less potent and even stimulated the growth of the tumors in the absence of estrogens thus, illustrating the stimulatory effect of tamoxifen on **breast cancer** growth. When incubated with human Ishikawa endometrial carcinoma cells, EM-800 had no stimulatory effect on alk. phosphatase activity, an estrogen-sensitive parameter. Raloxifene, Droloxifene, hydroxytoremifene and hydroxytamoxifen, all stimulated to various extents, the activity of this enzyme. The stimulatory effect of all four compds. was blocked by EM-800 thus, confirming their estrogenic activity in human endometrial tissue. When administered to ovariectomized **animals**, EM-800 prevents bone loss, the effect on bone mineral d., trabecular bone vol., and trabecular sepn. being 5-10 times more potent than that of raloxifene. EM-800 lowers serum cholesterol and triglyceride levels in the **rat**, as well as in women. The detailed information obtained at the preclin. level with EM-652 or EM-800 indicates that these orally active compds. are highly potent and pure antiestrogens in the mammary gland and endometrium while they prevent bone loss and lower serum cholesterol and triglyceride levels. Preclin. and clin. data clearly suggest the interest of studying this compd. in the neoadjuvant and adjuvant settings and, most importantly, for the prevention of breast and uterine cancer in which settings they should provide addnl. benefits by reducing bone loss and by decreasing serum cholesterol and triglyceride levels.

REFERENCE COUNT: 92 THERE ARE 92 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 10 OF 26 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:640146 CAPLUS
DOCUMENT NUMBER: 134:248846
TITLE: Anti-HER2 radioimmunotherapy
AUTHOR(S): Brechbiel, Martin W.; Waldmann, Thomas A.
CORPORATE SOURCE: Radioimmune and Inorganic Chemistry Section, Radiation Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, 20892-1374, USA
SOURCE: Breast Disease (**2000**), 11, 125-132
CODEN: BRDIE5; ISSN: 0888-6008
PUBLISHER: IOS Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A **review** w ith 50 refs. HER2/neu is a receptor protein whose over-expression strongly correlates with poor prognosis in breast carcinomas. It is used increasingly as a therapeutic target for breast carcinomas in clin. human trials. In particular, monoclonal antibodies (mAbs) that target HER2/neu have been investigated for therapeutic applications. Anti-Her2 mAbs linked to radionuclides have been used in pre-clin. models and in patients for radioimmunolocalization of tumors using external scintigraphy and intraoperative hand-held gamma detecting probes. Initial efforts of systemic radioimmunotherapy employed radio-iodinated mAbs. In a murine human **breast cancer** **xenograft** model, the radiolabeled mAb was 20-fold more effective than the unarmed mAb but did not yield permanent eradication of the tumor. Due to the limitations of radio-iodine (131I), metallic radionuclides (e.g, the .beta.--emmiter 90Y or the .alpha.-emitters 213Bi, 212Bi, 212Pb) linked to mAb's are being evaluated in murine models. Complete elimination of beast cancer **xenografts** was possible in an adjuvant setting using 212Pb linked to an anti-HER2/neu mAb. Finally, major efforts are underway to increase the access of the radiolabel to the tumor cell in large solid tumors. One such approach involved a pretargeting strategy with an initial administration of streptavidin linked to mAb that, after a clearing step, was followed by biotin armed with the radionuclide. Although major challenges must be addressed,

HER2/neu represents a very attractive target for systemic radioimmunotherapy of **breast cancer**.

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 11 OF 26 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:634609 CAPLUS
DOCUMENT NUMBER: 134:125979
TITLE: Peptides and antitumor activity: Development and investigation of some peptides with antitumor activity
AUTHOR(S): Teplan, I.
CORPORATE SOURCE: Department of Medical Chemistry, Semmelweis University of Medicine, Budapest, H-1088, Hung.
SOURCE: Acta Biologica Hungarica (**2000**), 51(1), 1-29
CODEN: ABHUE6; ISSN: 0236-5383
PUBLISHER: Akademiai Kiado
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A **review**, with 35 refs. We developed a group of synthetic analogs of GnRH and somatostatin to inhibit the tumor growth of different kind. The GnRH analogs decreasing the gonadotropin and steroid hormone levels act on the hormone dependent tumors and influence their growth. One of the most effective antitumor analog was patented under the name FOLLIGEN which inhibited the **breast cancer** caused by DMBA in **rats** without any side-effects. Other inhibitory analogs of GnRH with long-lasting effect were effective in the treatment of breast, ovary and prostate tumors. Another analog [.alpha.-Asp(DEA)]6,Gln8-hGnRH showed a very low endocrine but high antitumor effect in both in vitro and in vivo expts. Its tritium labeled deriv. exhibited specific binding sites on human tumor cell lines. We synthesized the analogs of GnRH-III with effective selective antitumor activity which does not alter the ovarian cycle of **rats** but inhibits the colony-formation of human **breast cancer** cell lines and has a significant antiproliferative effect. We also synthesized conjugates of potent GnRH analogs with a branched chain polylysine backbone which induce a 33-35% decrease of cell nos. of MCF-7 and MDA-MB-231 human **breast cancer** cell lines and 45-50% inhibition of cell proliferation. Another conjugate decreased the tumor growth of MDA-MB-231 **xenografts** by 80% in a treatment of 9 wk and even tumor free **animals** could be found among the ones treated. Using these radiolabeled peptide hormone analogs we found that human tumor cell lines and **xenografts** specifically bind the GnRH conjugates. We also synthesized a series of somatostatin analogs which inhibit tyrosine kinases and the growth of several breast, prostate and colon tumor cell lines. One of our best analogs was a heptapeptide, TT-232, which strongly inhibited the tyrosine kinase activity and the cell-proliferation in different colon tumor cells. However, it did not inhibit the growth hormone release either in vitro or in vivo from **rat** pituitary cells. The TT-232 was found to be effective on 60 human tumor cell lines, it significantly inhibited the tumor growth on different **animal** tumor models, and induced apoptosis, as a result of which some **animals** became tumor free. The TT-232 inhibited the tumor growth of PC3 prostate **xenografts** with 60% and caused a 100% survival of **mice** 60 days after the transplantation. It is being preclinically tested at present. We have shown that the new GnRH analogs acting without any hormonal effect and the Somatostatin analogs with strong antitumor and tyrosine kinase inhibitory activity but no hormonal effect may represent a breakthrough in the research of the antitumor peptides, having direct effect on tumor cells.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 12 OF 26 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:235622 CAPLUS

DOCUMENT NUMBER: 133:869
TITLE: DHEA, the precursor of androgens and estrogens in peripheral tissues in the human: intracrinology
AUTHOR(S): Labrie, Fernand; Belanger, Alain; Luu-The, Van; Labrie, Claude; Simard, Jacques; Lin, Sheng-Xiang
CORPORATE SOURCE: Oncology and Molecular Endocrinology Research Center, Laval University, Le Centre Hospitalier Universitaire de Quebec, Quebec, QC, G1V 4G2, Can.
SOURCE: Dehydroepiandrosterone (DHEA) (**2000**), 299-342. Editor(s): Kalimi, Mohammed; Regelson, William. Walter de Gruyter GmbH & Co. KG: Berlin, Germany.
CODEN: 68TYAR
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A **review**, with 167 refs. The following topics were discussed: mol. biol. of human steroidogenic enzymes; the decline in circulating DHEA with aging; stimulation of bone mineral d. by DHEA in **rats**; prevention of development of DMBA-induced mammary carcinoma in **rats**; inhibition of growth of human **breast cancer xenografts** in nude **mice**; effects of DHEA in postmenopausal women; and application of intracrinol. to the treatment of prostate cancer.
REFERENCE COUNT: 168 THERE ARE 168 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 13 OF 26 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:437555 CAPLUS
DOCUMENT NUMBER: 131:208327
TITLE: EM-652 (SCH 57068), a third generation SERM acting as pure antiestrogen in the mammary gland and endometrium
AUTHOR(S): Labrie, Fernand; Labrie, Claude; Belanger, Alain; Simard, Jacques; Gauthier, Sylvain; Luu-The, Van; Merand, Yves; Giguere, Vincent; Candas, Bernard; Luo, Shouqi; Martel, Celine; Singh, Shankar Mohan; Fournier, Marc; Coquet, Agnes; Richard, Virgile; Charbonneau, Ronald; Charpenet, Gilles; Tremblay, Andre; Tremblay, Gilles; Cusan, Lionel; Veilleux, Raymonde
CORPORATE SOURCE: Oncology and Molecular Endocrinology Research Center, Centre Hospitalier Universitaire de Quebec (CHUQ), Pavilion CHUL, Department of Medicine, Laval University, Quebec, QC, G1V 4G2, Can.
SOURCE: Journal of Steroid Biochemistry and Molecular Biology (**1999**), 69(1-6), 51-84
CODEN: JSBBEZ; ISSN: 0960-0760
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A **review**, with 224 refs. **Breast cancer** is the most frequent cancer in women while it is the second cause of cancer death. Estrogens are well recognized to play the predominant role in **breast cancer** development and growth and much efforts have been devoted to the blockade of estrogen formation and action. The most widely used therapy of **breast cancer** which has shown benefits at all stages of the disease is the use of the antiestrogen Tamoxifen. This compd., however, possesses mixed agonist and antagonist activity and major efforts have been devoted to the development of compds. having pure antiestrogenic activity in the mammary gland and endometrium. Such a compd. would avoid the problem of stimulation of the endometrium and the risk of endometrial carcinoma. We have thus synthesized an orally active non-steroidal antiestrogen, EM-652 (SCH 57068) and the prodrug EM-800 (SCH57050) which are the most potent of the known antiestrogens.

EM-652 is the compd. having the highest affinity for the estrogen receptor, including estradiol. It has higher affinity for the ER than ICI 182780, hydroxytamoxifen, raloxifene, droloxifene and hydroxytoremifene. EM-652 has the most potent inhibitory activity on both ER.alpha. and ER.beta. compared to any of the other antiestrogens tested. An important aspect of EM-652 is that it inhibits both the AF1 and AF2 functions of both ER.alpha. and ER.beta. while the inhibitory action of hydroxytamoxifen is limited to AF2, the ligand-dependent function of the estrogen receptors. AF1 activity is constitutive, ligand-independent and is responsible for mediation of the activity of growth factors and of the ras oncogene and MAP-kinase pathway. EM-652 inhibits Ras-induced transcriptional activity of ER.alpha. and ER.beta. and blocks SRC-1-stimulated activity of the two receptors. EM-652 was also found to block the recruitment of SRC-1 at AF1 of ER.beta., this ligand-independent activation of AF1 being closely related to phosphorylation of the steroid receptors by protein kinase. Most importantly, the antiestrogen hydroxytamoxifen has no inhibitory effect on the SRC-1-induced ER.beta. activity while the pure antiestrogen EM-652 completely abolishes this effect, thus strengthening the need to use pure antiestrogens in **breast cancer** therapy in order to control all known aspects of ER-regulated gene expression. In fact, the absence of blockade of AF2 by hydroxytamoxifen could explain why the benefits of tamoxifen obsd. up to 5 yr become neg. at longer time intervals and why resistance develops to tamoxifen. EM-800, the prodrug of EM-652, has been shown to prevent the development of dimethylbenz(a)anthracene (DMBA)-induced mammary carcinoma in the **rat**, a well-recognized model of human **breast cancer**. It is of interest that the addn. of dehydroepiandrosterone, a precursor of androgens, to EM-800, led to complete inhibition of tumor development in this model. Not only the development, but also the growth of established DMBA-induced mammary carcinoma was inhibited by treatment with EM-800. An inhibitory effect was also obsd. when medroxyprogesterone was added to treatment with EM-800. Uterine size was reduced to castration levels in the groups of **animals** treated with EM-800. An almost complete disappearance of estrogen receptors was obsd. in the uterus, vaginum and tumors in nude **mice** treated with EM-800. EM-652 was the most potent antiestrogen to inhibit the growth of human **breast cancer** ZR-75-1, MCF-7 and T-47D cells in vitro when compared with ICI 182780, ICI 164384, hydroxytamoxifen, and droloxifene. Moreover, EM-652 and EM-800 have no stimulatory effect on the basal levels of cell proliferation in the absence of E2 while hydroxytamoxifen and droloxifene had a stimulatory effect on the basal growth of T-47D and ZR-75-1 cells. EM-652 was also the most potent inhibitor of the percentage of cycling cancer cells. When human **breast cancer** ZR-75-1 **xenografts** were grown in nude **mice**, EM-800 led to a complete inhibition of the stimulatory effect of estrogens in ovariectomized **mice** while tamoxifen was less potent and even stimulated the growth of the tumors in the absence of estrogens, thus illustrating the stimulatory effect of tamoxifen on **breast cancer** growth. When incubated with human Ishikawa endometrial carcinoma cells, EM-800 had no stimulatory effect on alk. phosphatase activity, an estrogen-sensitive parameter. Raloxifene, droloxifene, hydroxytoremifene and hydroxytamoxifen, on the other hand, all stimulated to various extent, the activity of this enzyme. The stimulatory effect of all four compds. was blocked by EM-800, thus confirming their estrogenic activity in human endometrial tissue. When administered to ovariectomized **animals**, EM-800 prevents bone loss, the effect on bone mineral d., trabecular bone vol., and trabecular sepn. being 5-10 times more potent than raloxifene. EM-800 lowers serum cholesterol and triglyceride levels in the **rat** as well as in women. In a Phase II study performed in patients with **breast cancer** showing failure on tamoxifen, 1 patient had a complete response while 5 patients had a partial response and stable disease for at least three months has been obsd. in an addnl. 13 patients for a total of 19 pos. responses out of 43 evaluable patients (44.2%). No significant

secondary effect related to the drug was obsd. A phase 3 international clin. trial is currently being performed in tamoxifen failure patients where EM-800 (SCH 57050) is compared to Arimidex. The detailed information obtained at the preclin. level with EM-652 or EM-800 indicates that these orally active compds. are highly potent and pure antiestrogens in the mammary gland and endometrium while they prevent bone loss and lower serum cholesterol and triglyceride levels. Preclin. and clin. data clearly suggest the interest of studying this compd. in the neoadjuvant and adjuvant settings and, most importantly, for the prevention of breast and uterine cancer in which settings they should provide addnl. benefits on bone and lipids.

REFERENCE COUNT: 224 THERE ARE 224 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 14 OF 26 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:133097 CAPLUS
DOCUMENT NUMBER: 130:337312
TITLE: Inhibition of human **breast cancer** cell growth and metastasis in nude **mice** by citrus juices and their constituent flavonoids
AUTHOR(S): Guthrie, Najla; Carroll, Kenneth K.
CORPORATE SOURCE: Centre For Human Nutrition, Department of Biochemistry, University of Western Ontario, London, ON, N6A 5C1, Can.
SOURCE: Biological Oxidants and Antioxidants (**1998**), 310-316. Editor(s): Packer, Lester; Ong, Augustine S. H. AOCS Press: Champaign, Ill.
CODEN: 67ILAS
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A **review** with 19 refs. The topics include citrus juice flavonoids effects on human **breast cancer** cells in culture, **review** of studies on mechanism of flavonoids action, and studies in **animal breast cancer** models (chem. induced and **xenografts**).
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 15 OF 26 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:17476 CAPLUS
DOCUMENT NUMBER: 130:231718
TITLE: Targeting of drugs to solid tumors using anti-HER2 immunoliposomes
AUTHOR(S): Papahadjopoulos, Demetrios; Kirpotin, Dmitri B.; Park, John W.; Hong, Keelung; Shao, Yi; Shalaby, Refaat; Colbern, Gail; Benz, Christopher C.
CORPORATE SOURCE: California Pacific Medical Center Research Institute, San Francisco, CA, 94115, USA
SOURCE: Journal of Liposome Research (**1998**), 8(4), 425-442
CODEN: JLREE7; ISSN: 0898-2104
PUBLISHER: Marcel Dekker, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A **review** with 76 refs. Cancer therapy would clearly benefit from a carrier system capable of intracellular delivery of systemically administered drugs to cancer cells in solid tumors. Sterically stabilized immunoliposomes specific to the cells expressing HER2 protooncogene (anti-HER2 SIL), were designed by conjugating Fab' fragments of a recombinant humanized anti-HER2 MAb to the distal termini of poly(ethylene glycol) chains on the surface of unilamellar liposomes (size 90-100 nm) of phosphatidylcholine, cholesterol, and poly (ethylene glycol)-derivatized phosphatidylethanolamine. Anti-HER2 SIL avidly and specifically bound to

cultured HER2-overexpressing cancer cells (8,000-23,000 vesicles per cell) and became endocytosed (ke = 0.022-0.033 min.-1) via the coated pit pathway. Anti-HER2 SIL showed prolonged circulation lifetime in **rats** (blood MRT approx. 24 h) and significantly increased antitumor activity of encapsulated doxorubicin against HER2-overexpressing human **breast cancer xenografts** in nude **mice**. Although the accumulation of anti-HER2 SIL in HER2-overexpressing tumor **xenografts** was not increased over that of non-targeted sterically stabilized liposomes (SL), microscopic examn. revealed abundance of anti-HER2 SIL in the interstitial spaces, as well as within the cytoplasm of cancer cells, while identical liposomes lacking anti-HER2 Fab' were located predominantly within tumor-resident macrophages. Anti-HER2 SIL, a targeted vehicle capable of in vivo intracellular delivery of substances to HER2-overexpressing solid cancers, enhances the potential for tumor targeting and opens new avenues for better treatment of cancer.

REFERENCE COUNT: 76 THERE ARE 76 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 16 OF 26 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:723268 CAPLUS
DOCUMENT NUMBER: 130:263172
TITLE: Ah receptor agonists as endocrine disruptors: antiestrogenic activity and mechanisms
AUTHOR(S): Safe, S.; Wang, F.; Porter, W.; Duan, R.; McDougal, A.
CORPORATE SOURCE: Dep. Veterinary Physiology and Pharmacology, Texas A&M Univ., College Station, TX, 77843-4466, USA
SOURCE: Toxicology Letters (**1998**), 102-103, 343-347
CODEN: TOLED5; ISSN: 0378-4274
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A **review** with 13 refs. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) and related compds. induce a broad spectrum of biochem. and toxic responses and disrupt multiple endocrine pathways. Research in this lab. has focused on characterizing aryl hydrocarbon receptor (AhR)-mediated antiestrogenicity in the rodent uterus and mammary and in human **breast cancer** cells. TCDD inhibits multiple estrogen (E2)-induced responses in these tissues including development or growth of human mammary and endometrial cancer cells, carcinogen-induced mammary cancer in **rats**, and mammary cancer in **mice** bearing **breast cancer** cell **xenografts**. The mechanisms of AhR-mediated antiestrogenicity are complex; however, studies on the mol. biol. of cross-talk between the AhR and estrogen-receptor (ER) signaling pathways have been initiated using several E2-regulated genes as models. The results indicate that the nuclear AhR complex targets specific genomic core inhibitory dioxin responsive elements (iDREs) in promoter regions of some E2-responsive target genes to inhibit hormone-induced transactivation. The pS2, cathepsin and c-fos genes have functional iDREs, whereas the iDRE in the progesterone receptor gene promoter was not functional. Research has also focused on development of AhR-based antiestrogens which inhibit mammary tumor development and growth but do not exhibit prototypical AhR-induced toxic responses.

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 17 OF 26 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:363293 CAPLUS
DOCUMENT NUMBER: 129:90485
TITLE: DHEA and the intracrine formation of androgens and estrogens in peripheral target tissues: its role during aging
AUTHOR(S): Labrie, Fernand; Belanger, Alain; Luu-The, Van; Labrie, Claude; Simard, Jacques; Cusan, Leonello;

Gomez, Jose-Luis; Candas, Bernard
CORPORATE SOURCE: Laboratory of Molecular Endocrinology, CHUL (Le Centre Hospitalier de l'Universite Laval) Research Center and Laval University, Quebec, QC, G1V 4G2, Can.
SOURCE: Steroids (**1998**), 63(5/6), 322-328
CODEN: STEDAM; ISSN: 0039-128X
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A **review**, with 36 refs. Human and some other primates are unique since their adrenals secrete large amts. of dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S), which are converted into androstenedione (4-dione) and then into potent androgens and estrogens in peripheral tissues, therefore providing autonomous intracrine control to target tissues that can adjust the formation and metab. of active sex steroids according to local requirements. Knowledge in this area has recently made rapid progress with the elucidation of the structure of most of the tissue-specific cDNAs and genes that encode the steroidogenic enzymes responsible for the transformation of these inactive precursor steroids into androgens and/or estrogens. It is estd. that 30 to 50% of total androgens in men are synthesized in peripheral intracrine tissues from inactive adrenal precursors while, in women, peripheral estrogen formation is even more important, the best est. being 75% before menopause and 100% after menopause. The marked redn. in the formation of DHEA-S by the adrenals during aging, esp. before the age of 50 yr, results in a dramatic fall in the formation of active sex steroids in peripheral target tissues, a situation which is thought to be assocd. with a long series of age-related decreases such as insulin resistance, obesity, osteoporosis, cardiovascular diseases, loss of muscle mass, cancer and other diseases. The authors have demonstrated for the first time a series of medically important beneficial effects of DHEA administered for 12 mo to post-menopausal women. Most interestingly, the bone mineral d. significantly increased. This relatively rapid change was assocd. with an increase in plasma osteocalcin, a marker of bone formation, while a decrease in bone resorption reflected by a decrease in urinary hydroxyproline excretion was obsd. in parallel. In addn., the estrogenic stimulation of vaginal cytol. in the absence of any sign of stimulatory effect on the endometrium is also of potentially major interest for the prevention and management of menopause. Furthermore, the inhibitory effect of DHEA on the growth of human **breast cancer xenografts** in vivo in nude **mice** supports the beneficial use of DHEA as hormone replacement therapy in women.

L35 ANSWER 18 OF 26 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:238200 BIOSIS
DOCUMENT NUMBER: PREV200000238200
TITLE: Insights into tumor vascularization using magnetic resonance imaging and spectroscopy.
AUTHOR(S): Bhujwalla, Z. M. (1); Artemov, D.; Solaiyappan, M.
CORPORATE SOURCE: (1) Oncology Section, Division of MR Research, Department of Radiology, Johns Hopkins University School of Medicine, Baltimore, MD, 21205 USA
SOURCE: Eksperimental'naya Onkologiya, (**March, 2000**) Vol. 22, No. 1-2, pp. 3-7.
ISSN: 0204-3564.
DOCUMENT TYPE: General Review
LANGUAGE: English
SUMMARY LANGUAGE: English; Ukrainian

AB Magnetic resonance (MR) imaging (I) and spectrscopy (S) have a unique role to play in understanding the interplay between tumor metabolism and vascularization. The noninvasive nature of the technique allows investigation of the dynamics of this relationship both with growth and following treatment. Here we briefly **review** tumor vascularization and present data to demonstrate how MRI/MRS can provide

unique insight into tumor vascularization.

L35 ANSWER 19 OF 26 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002103408 EMBASE
TITLE: Trastuzumab in the treatment of non-small cell lung cancer.
AUTHOR: Azzoli C.G.; Krug L.M.; Miller V.A.; Kris M.G.; Mass R.
CORPORATE SOURCE: Dr. L.M. Krug, Memorial Sloan-Kettering Can. Center, 1275 York Ave, New York, NY 10021, United States
SOURCE: Seminars in Oncology, (2002) 29/1 SUPPL. 4 (59-65).
Refs: 46
ISSN: 0093-7754 CODEN: SOLGAV
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis
016 Cancer
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Trastuzumab is a humanized monoclonal antibody that binds to human epidermal growth factor-2 (HER2) and is approved by the US Food and Drug Administration for the treatment of advanced **breast cancer** that overexpresses HER2/neu protein. Preclinical data suggests a role for trastuzumab in the treatment of non-small cell lung cancer (NSCLC). HER2 protein is overexpressed in 20% to 66% of resected NSCLC tumors, and has been shown to predict poor patient outcome in multiple series. Experiments with NSCLC cell lines show that HER2 overexpression increases chemoresistance, invasiveness, and metastatic potential of the cells. In mouse **xenograft** experiments, trastuzumab halts tumor growth and is synergistic with cytotoxic chemotherapy. Ongoing phase II trials are showing that trastuzumab can be added to standard chemotherapy in the treatment of patients with advanced NSCLC without additional toxicity, and with promising efficacy. Whether trastuzumab will show a clear benefit for patients with NSCLC, either alone or in combination with established chemotherapy, remains to be proven in phase III testing.

L35 ANSWER 20 OF 26 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001377446 EMBASE
TITLE: A prevention strategy for circumventing drug resistance in cancer chemotherapy.
AUTHOR: Frenkel G.D.; Caffrey P.B.
CORPORATE SOURCE: G.D. Frenkel, Department of Biological Sciences, Rutgers University, Newark, NJ 07102, United States.
frenkel@andromeda.rutgers.edu
SOURCE: Current Pharmaceutical Design, (2001) 7/16 (1595-1614).
Refs: 243
ISSN: 1381-6128 CODEN: CPDEFP
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 010 Obstetrics and Gynecology
015 Chest Diseases, Thoracic Surgery and Tuberculosis
016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The development of drug resistance is considered to be a major cause for the failure of chemotherapy in a number of types of cancer, including ovarian, breast and lung. Most previous research has focused on approaches to reverse drug resistance once it has arisen, that is, on the use of agents which can make drug-resistant tumors more sensitive to

chemotherapy. Unfortunately, this approach has thus far met with only limited clinical success. Because of the prevalence of drug resistance in cases of advanced cancer, there exists an urgent need to develop new approaches to dealing with this problem. We have hypothesized the feasibility of an alternative approach: the use of specific agents to prevent the development of resistance before it arises. Our initial studies to examine this hypothesis have focused on ovarian cancer. We have designed both in vitro and in vivo systems in which resistance develops rapidly after exposure of tumor cells or **xenografts** to melphalan or cisplatin. Using these systems we have shown that two selenium compounds, selenite and selenomethionine are able to prevent the induction of resistance. Furthermore, inclusion of selenite in a chemotherapeutic protocol can result in a significant enhancement of the efficacy of cisplatin in suppressing the growth of human ovarian tumor **xenografts**. These results have supported the idea that prevention may be a useful new approach to the problem of drug resistance in cancer chemotherapy.

L35 ANSWER 21 OF 26 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001154080 EMBASE
TITLE: Pure selective estrogen receptor modulators, new molecules having absolute cell specificity ranging from pure antiestrogenic to complete estrogen-like activities.
AUTHOR: Labrie F.; Labrie C.; Belanger A.; Giguere V.; Simard J.; Merand Y.; Gauthier S.; Luu-The V.; Candas B.; Martel C.; Luo S.
CORPORATE SOURCE: F. Labrie, Oncol./Molec. Endocrinol. Res. Ctr., Laval Univ. Medical Center (CHUL), Quebec G1V 4G2, Canada
SOURCE: Advances in Protein Chemistry, (2001) 56/- (293-368).
Refs: 344
ISSN: 0065-3233 CODEN: APCHA2
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English

L35 ANSWER 22 OF 26 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001090052 EMBASE
TITLE: Development of ABX-EGF, a fully human anti-EGF receptor monoclonal antibody, for cancer therapy.
AUTHOR: Yang X.-D.; Jia X.-C.; Corvalan J.R.F.; Wang P.; Davis C.G.
CORPORATE SOURCE: X.D. Yang, Abgenix Inc., 7601 Dumbarton Circle, Fremont, CA 94555, United States
SOURCE: Critical Reviews in Oncology/Hematology, (2001) 38/1 (17-23).
Refs: 24
ISSN: 1040-8428 CODEN: CCRHEC
PUBLISHER IDENT.: S 1040-8428(00)00134-7
COUNTRY: Ireland
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
037 Drug Literature Index
005 General Pathology and Pathological Anatomy
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Overexpression of epidermal growth factor receptor (EGFr) has been demonstrated on many human tumors, and the increase in receptor expression levels has been linked with a poor clinical prognosis. Blocking the interaction of EGFr and the growth factors could lead to the arrest of

tumor growth and possibly result in tumor cell death. To this end, using XenoMouse.RTM. technology, ABX-EGF, a human IgG2 monoclonal antibody (mAb) specific to human EGFr, has been generated. ABX-EGF binds EGFr with high affinity (5x10(-11) M), blocks the binding of both EGF and transforming growth factor-.alpha. (TGF-.alpha.) to various EGFr-expressing human carcinoma cell lines, and inhibits EGF-dependent tumor cell activation, including EGFr tyrosine phosphorylation, increased extracellular acidification rate, and cell proliferation. In vivo ABX-EGF prevents completely the formation of human epidermoid carcinoma A431 **xenografts** in athymic **mice**. More importantly, administration of ABX-EGF without concomitant chemotherapy results in complete eradication of established tumors. No tumor recurrence was observed for more than 8 months following the last antibody injection, further indicating complete tumor cell elimination by the antibody. Inhibition of human pancreatic, renal, breast and prostate tumor **xenografts** which express different levels of EGFr by ABX-EGF was also achieved. Tumor expressing more than 17 000 EGFr molecules per cell showed significant growth inhibition when treated with ABX-EGF. ABX-EGF had no effect on EGFr-negative tumors. The potency of ABX-EGF in eradicating well-established tumors without concomitant chemotherapy indicates its potential as a monotherapeutic agent for treatment of multiple EGFr-expressing human solid tumors, including those where no effective chemotherapy is available. Utilization of mAbs directed to growth factor receptors as cancer therapeutics has been validated recently by the tumor responses obtained from clinical trials with Herceptin, the humanized anti-HER2 antibody, in patients with HER2 overexpressing metastatic **breast cancer**. Being a fully human antibody, ABX-EGF is anticipated to exhibit a long serum half-life and minimal immunogenicity with repeated administration, even in immunocompetent patients. These results demonstrate the potent anti-tumor activity of ABX-EGF and its therapeutic potential for the treatment of multiple human solid tumors that overexpress EGFr. Copyright .COPYRGT. 2001 Elsevier Science Ireland Ltd.

L35 ANSWER 23 OF 26 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001029028 EMBASE
TITLE: HER2/neu antisense targeting of human breast carcinoma.
AUTHOR: Roh H.; Pippin J.A.; Green D.W.; Boswell C.B.; Hirose C.T.; Mokadam N.; Drebin J.A.
CORPORATE SOURCE: J.A. Drebin, Washington Univ. School of Medicine, Campus Box 8109, Saint Louis, MO 63110, United States
SOURCE: Oncogene, (11 Dec 2000) 19/53 (6138-6143).
Refs: 34
ISSN: 0950-9232 CODEN: ONCNES
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Overexpression of the HER2/neu oncogene is observed in approximately 30% of human breast carcinoma specimens. HER2/neu overexpression is a negative prognostic factor in **breast cancer** patients. Cancer cells that overexpress HER2/neu may also be less sensitive to chemotherapy. In order to further define mechanisms by which HER2/neu overexpression drives neoplastic cell growth and chemoresistance, antisense oligonucleotides (ODNs) have been utilized to selectively down-regulate HER2/neu expression in human **breast cancer** cells. Such antisense ODNs suppress HER2/neu mRNA and protein levels in a dose-dependent, sequence-specific manner. Down-regulation of HER2/neu expression in HER2/neu overexpressing **breast cancer** cells inhibits cell cycle progression in G(0)/G(1) and results in apoptotic cell death. In tissue culture studies, combined treatment of HER2/neu overexpressing **breast cancer** cells with HER2/neu antisense ODNs and conventional chemotherapeutic agents results

in synergistic inhibition of cancer cell growth and activation of apoptotic cell death mechanisms. These studies have been extended to demonstrate synergistic antitumor effects following systemic treatment with antisense ODNs plus doxorubicin in nude **mice** bearing human breast carcinoma **xenografts**. Collectively these findings demonstrate that HER2/neu overexpression stimulates anti-apoptotic cell survival mechanisms and suggest that HER2/neu antisense ODNs may be of use in cancer therapeutics.

L35 ANSWER 24 OF 26 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000271731 EMBASE
TITLE: Emerging antibody-based HER2 (ErbB-2/neu) therapeutics.
AUTHOR: Krauss W.C.; Park J.W.; Kirpotin D.B.; Hong K.; Benz C.C.
CORPORATE SOURCE: Dr. C.C. Benz, Division of Hematology-Oncology, University of California, Department of Medicine, 505 Parnassus Ave., San Francisco, CA 94143-1270, United States.
benz@itsa.ucsf.edu
SOURCE: Breast Disease, (2000) 11/- (113-124).
Refs: 65
ISSN: 0888-6008 CODEN: BRDIE5
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
022 Human Genetics
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Targeting HER2(ErbB-2/neu) overexpressing tumor cells to selectively deliver anticancer agents and thereby reduce host toxicity represents a rational and emerging strategy for the treatment of breast and other epithelial cancers. The extracellular domain of the HER2 receptor tyrosine kinase is readily accessible to systemically administered antibody-based therapeutics, including growth-inhibiting monclonals such as rhuMAbHER2 (trastuzmab/Herceptin(C)) as well as anti-HER2 immunotoxins, antibody-dependent enzyme prodrug therapy (ADEPT), and immune cell recruiting bispecific antibodies. In addition to summarizing recent advances in these antibody-based strategies, this **review** focuses on preclinical advances in the development of anti-HER2 immunoliposomes (ILs) as a platform technology for targeted drug delivery. Extensive in vitro and in vivo testing including efficacy and tumor uptake studies in multiple human tumor **xenograft** models now provide conclusive evidence for the superior therapeutic efficacy of anti-HER2 ILs-doxorubicin (dox) over free dox or liposomal (Ls)-dox, and even over combinations of dox and Ls-dox with rhuMAbHER2. As anti-HER2 ILs-dox approaches clinical testing in patients with advanced HER2 overexpressing **breast cancer**, future applications of this novel targeting strategy will also broaden to include intracellular delivery of other anticancer agents as well as therapeutic nucleic acids (oligonucleotides, genes).

L35 ANSWER 25 OF 26 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999403678 EMBASE
TITLE: Biologically-active gold(III) complexes.
AUTHOR: Parish R.V.
CORPORATE SOURCE: R.V. Parish, Department of Chemistry, UMIST, Manchester M60 1QD, United Kingdom
SOURCE: Metal-Based Drugs, (1999) 6/4-5 (271-276).
Refs: 18
ISSN: 0793-0291 CODEN: MBADEI
COUNTRY: Israel
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
030 Pharmacology

037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB A **review** is given of the background to and results of the succesful pharmacological testing of [AuX2(damp)] (X = Cl, OAc; damp = 2-Me2NCH2C6H4) against a range of microbes, fungi and tumours, culminating in in vivo **xenografts** of ZR-1-75. These are the first fully evaluated gold(III) complexes. The activity and reactions of the diacetato-complex bear a resemblance to cisplatin, and some of the relevant chemistry is discussed. Preliminary screening data for C,P-chelated tertiary phosphine derivatives of gold(III) are presented.

L35 ANSWER 26 OF 26 EMBASE
ACCESSION NUMBER: 1999151827 EMBASE
TITLE: Azelaic acid : Potential as a general antitumoural agent.
AUTHOR: Breathnach A.S.
CORPORATE SOURCE: A.S. Breathnach, 4 Pelhams Close, Esher, Surrey KT10 8QB, United Kingdom
SOURCE: Medical Hypotheses, (1999) 52/3 (221-226).
Refs: 52
ISSN: 0306-9877 CODEN: MEHYDY
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Azelaic acid is a naturally occurring straight-chained 9-carbon atom dicarboxylic acid which is non-toxic, non-teratogenic, and non-mutagenic. Its antiproliferative and cytotoxic effect on a variety of tumoural cell lines in culture, due to inhibition of mitochondrial oxidoreductases of the respiratory chain and of enzymes concerned with DNA synthesis is well established; normal cells are unaffected at similar dosages and times of exposure. Human melanoma cells xenotransplanted onto athymic nude **mice** are significantly affected by administration of azelaic acid. Clinically, in humans, it has already been shown to cause regression of melanoma in situ and primary invasive malignant melanoma. These results rank azelaic acid as a potential general antitumoural agent. It can be administered topically, focally, orally, intravenously, intra-arterially, and intralymphatically, all without local or general ill-effects, and is metabolized without harmful side-products. Simultaneous administration by different routes can ensure delivery of high concentrations at lesional sites and for sustained periods. Courses can be repeated. In addition to melanoma, cutaneous and bronchial squamous cell carcinoma, bladder and **breast cancers**, and leukaemia would seem to be ideal candidates for further clinical investigation and trial of the anti-cancer potential of azelaic acid, as prime, adjuvant, and palliative therapy, and for disseminated disease.